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ANNALS OF
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VOLUME 14 SEPTEMBER, 1940 NUMBER 3

OBSERVATIONS UPON THE EFFECT OF CORAMINE IN CERTAIN CARDIAC STATES *

By WILLIAM D. STROUD, M.D., F.A.C.P., and PAUL H. TWADDLE, M.D.,
Philadelphia, Pennsylvania

THERE is considerable evidence in the literature [1, 2] that Coramine (Ciba), a 25 per cent aqueous solution of the diethylamide of pyridine beta carboxylic acid, has been established as a valuable agent in the treatment of cerebral and respiratory depression due to poisoning by the barbiturates, avertin, alcohol, opiates, etc. There is little conclusive evidence concerning its action on the circulatory system [2, 3] or on the respiratory distress of heart disease, although there appears to be a definite impression that benefit does follow its use. Objective evidence to explain the symptomatic response has not been striking.

A number of independent observers [4, 5, 6, 7 and others] have shown, by animal experimentation, that Coramine acts as a coronary dilator, and Stoland and Ginsberg [4] have concluded that in dogs small doses are effective as a general vascular dilator while large doses are more effective as a coronary dilator. Such findings in animals with apparently healthy vascular tissue unfortunately can not be transferred directly to humans with diseased arteries. Wright [8] has been unable, using Coramine, to demonstrate appreciable changes in the peripheral vascular circulation in man in spite of the fact that Massart [9] concludes from observations on the intact dog that this drug causes a generalized arterial relaxation.

Other measurable objective data are meager. Frommel [10] found in electrocardiographic studies a shortening of conduction time (P–R interval) in frogs, guinea pigs and rabbits when non-toxic doses were used. Eisner [11] studied the effect on conductivity in clinical material and reported no change with Coramine. Cowan [12] believes he obtained an increased voltage in the first ventricular complex, but notes variable changes in the T-waves.

Concerning the blood pressure and pulse rate changes there have been

* Read at the Cleveland meeting of the American College of Physicians, April 4, 1940.

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conflicting reports.[4, 13, 14, etc.] Lerner,[15] although noting symptomatic improvement and at times striking relief of edema, was unable to find significant blood pressure or pulse rate changes. Frommel[10] noted a decreased heart rate in frogs, but an increase in guinea pigs and rabbits. The observations of Schube[14] (who used Coramine to control the narcosis produced by barbiturates), probably represents the predominant opinion in the literature when he states: "the pulse rate and volume in no individual were altered appreciably by Coramine. Likewise the blood pressure was not altered appreciably, regardless of whether arteriosclerosis was present or absent, and irrespective of the presence of normal, low or high pressure." It is probable, as Henderson states,[3] that "blood pressure may rise as a secondary consequence of improved respirations and partly due to the general stimulant effect on the reflex centers, of which the vasomotor center is one."

Mention is occasionally made of diuresis following treatment with Coramine, but this factor has not been stressed either in a positive or negative manner. We have not been able to find records of vital capacity or of blood circulation time in cases with cardiac disease receiving Coramine, nor have we noted studies of intrathecal pressure changes. Schlösser and Schwarz,[32] as a result of the use of Cardiazol and Coramine, noted a significant lowering of venous pressure, in most of their cases with cardiac failure, simultaneous with subjective improvement.

Our purpose has been to observe the effects of Coramine on patients with cardiac disease investigating particularly its action in cases with respiratory distress. Four groups of patients were selected for these studies: *Group 1:* The effect on severe respiratory distress. *Group 2:* The effect on certain signs which might reflect cardiac efficiency. *Group 3:* The effect on intrathecal pressure. *Group 4:* The effect on venous pressure.

Effect on Respiratory Distress

A group of patients have been selected who presented themselves with evident respiratory embarrassment, and in whom it was felt that response could be measured by disappearance of Cheyne-Stokes respirations, or a lessening in the number and severity of attacks of paroxysmal dyspnea. *Thirteen* trials were conducted on *ten* patients. The case histories are presented in this report, and table 1 summarizes the results. In most instances Coramine was administered by mouth in doses of 3 to 5 c.c., and repeated four or five times daily, although in two cases (2 and 4) it was given intramuscularly, and in one case (7) oral administration was preceded by a single intravenous injection. The response in cases 3 and 26 was insignificant, and case 5 on one trial (Nov. 1938) failed to derive any relief. In seven instances which responded to Coramine, an attempt was made to control the response by temporary withdrawal of the medication. Upon withdrawal of Coramine from these cases (1, 2, 4, 5 (March 1939), 7, 8, 25) six

TABLE I

Effect of Coramine in Treatment of Cardiac Respiratory Distress

Case Number	Diagnosis	Type of Distress	Dosage	Results	Effect of Withdrawal	Again Started Coramine	Effect
1	Art. scl. hypertension; CE; frequent P.B.; MI; Class IV	Paroxysmal nocturnal dyspnea, 7–11 attacks q.n.	3 c.c. p.o. 5 i.d. for 4 days	Marked symptomatic response, and attacks reduced to 3	Attacks increased to 7–8–14 on successive nights	3 c.c. p.o. 5 i.d. for 10 days	Diminishing attacks on successive nights 8, 8, 8, 4, 0, 0, 0, 0, 0, 0
2	Art. scl. hypertension; CE; premature beats; MI; Class IV	Cheyne-Stokes (Cardiac psychosis)	5 c.c. i.m. q 4 h. 4 days	Slept 1st night. In 24–48 hrs. normal breathing for ¾–2 hrs. after each dose. After 48 hrs. normal resp.	No recurrence of Cheyne-Stokes in 2 days. Patient died with coronary closure		
3	Art. scl. hypertension; CE; gallop rhythm; MI; Class IV	Cheyne-Stokes. (No orthopnea)	3 c.c. p.o. 5 i.d. 7 days, 3 c.c. i.m. 4 days	Cheyne-Stokes not controlled until 6th day. Reverted to Cheyne-Stokes on 8th day with increased failure			
4	Rh.H.D.; CE; AS, AI, MI, gallop rhythm; Class IV	Paroxysmal nocturnal dyspnea. Cheyne-Stokes	5 c.c. i.m. 7.30 p.m. and 10 p.m.	Slept without attack	Cheyne-Stokes recurred next day. Increased dyspnea	5 c.c. i.v. and 4 hrs. later 5 c.c. i.m.	No further respiratory distress
5	Art. scl. hypertension; CE; premature beats; MI; Class IV	Sept. 1938, paroxysmal dyspnea Nov. 1938 Cheyne-Stokes (Cardiac psychosis)	3 c.c. p.o. 4 i.d. 15 days 3 c.c. p.o. 4 i.d. 22 days	After 24 hrs. fewer attacks. After 48 hrs. complete relief No relief			

TABLE I—*Continued*

Case Number	Diagnosis	Type of Distress	Dosage	Results	Effect of Withdrawal	Again Started Coramine	Effect
5	Art. scl. hypertension; CE; premature beats; MI; Class IV	Feb. 1939 Cheyne-Stokes severe dyspnea. (O.P.D.)	4 c.c. p.o. 4 i.d. 3 wks.	Cheyne-Stokes relieved in 24 hrs. Dyspnea gone in 2 wks. Worse after 3 wks. with failure and dig. toxic			
		March 1939 Cheyne-Stokes	4 c.c. p.o. 5 i.d. 4 days	Regular breathing within 24 hrs.	Reverted to Cheyne-Stokes in 3 days		
6	Art. scl. hypertension; CE; NSR; MI; Class IV	Cheyne-Stokes 3 attacks in 6 mo.	2 c.c. p.o. 4 i.d.	Cheyne-Stokes controlled in 24–48 hrs.			
7	Art. scl. hypertension; CE; gallop rhythm; Class IV	Cheyne-Stokes (Cardiac psychosis)	5 c.c. i.v. then 3 c.c. p.o. q 3 h 5 days	On 2d day normal breathing followed Coramine for 1½–2 hrs. From 3–5 days normal	Reverted to Cheyne-Stokes in 2 days	3 c.c. p.o. q 3 h.	Normal after 24 hours of this drug
8	Art. scl. hypertension; CE, NSR; MI; Class IV	Paroxysmal dyspnea	4 c.c. p.o. 5 i.d. 4 days	Decreased number and severity of attacks. None after 2d day (Nausea)	Severe paroxysmal attacks in 2 days	3 c.c. p.o. 5 i.d.	No attacks after 12 hrs. Temporary withdrawal on 13th day and had attacks next day
25	Art. scl. hypertension; CE; NSR; MI; Class IV. Recent hemiplegia	Cheyne-Stokes	4 c.c. p.o. 5 i.d. 5 doses	Normal breathing, within 24 hrs.	Reverted to Cheyne-Stokes in 8 hrs.	4 c.c. p.o. 5 i.d. 1 day then 3 c.c. p.o. 5 i.d. 10 days	Normal respirations except for hiccoughs and temporary nausea
26	Art. scl.; CE; occasional P.B.; MI; Class IV	Cheyne-Stokes	4 c.c. p.o. 5 i.d. 7 days	No relief			

of them reverted to their respiratory distress within 8 hours to 3 days; the remaining case (2) died from coronary closure two days after treatment was interrupted. Five of these patients were then given Coramine again and relief of distress was soon evident. The delayed response in case 1 would throw doubt on the correlation between the relief of paroxysmal dyspnea and treatment, but we are inclined to credit Coramine in view of a more prompt relief of disturbing dyspnea, return of appetite, etc. In cases 5 (Sept. 1938), 5 (Feb. 1939) and 6 improvement was evident following the use of Coramine but there are no adequate controls so that the results are merely suggestive. A review of these cases shows that in five trials there were favorable responses which were controlled, in five trials there was evident benefit but control was unsatisfactory, while the response was negligible in the remaining three trials.

Effect on Signs of Cardiac Efficiency

A second group of patients with moderate congestive heart failure were studied objectively to observe if any notable change resulted following the use of Coramine given orally, which might reflect cardiac efficiency. None of this group had received digitalis during the month preceding these observations, and four or more days of bed rest with sedation and limited measured fluid intake were allowed. Record was made of variations in the arterial blood pressure, blood circulation time (using saccharin in 100 per cent solution—arm to tongue time), pulse rate, vital capacity and electrocardiograms; evidence of diuresis was noted as indicated by volume output of urine, in relation to constant intake, and by change in weight. Readings were made at intervals of not more than four days. Table 2 explains these findings. Allowing for the influence of bed rest, there has been no evidence of constant improvement in cardiac efficiency with Coramine.

Effect on Intrathecal Pressure

W. G. Harrison, Jr.[16] demonstrated that the intrathecal pressure of patients with congestive heart failure was greatly elevated; that the venous pressure showed a similar elevation above normal; and that changes in the pressure of one are usually paralleled by changes in the other. By withdrawal of sufficient spinal fluid to lower considerably the intrathecal pressure, he was able to observe a resulting lowering in the venous pressure in 8 out of 13 cases, and in a larger number there was evident symptomatic improvement. Following the example of Greene, Paul and Feller[17] who showed changes in intrathecal pressure and venous pressure as a result of treatment with theophyllin with ethylene-diamine (aminophyllin), we are studying cases to observe the response to the use of Coramine. Intrathecal pressure changes have been recorded on seven patients. In each case the patient was placed on his side on a stretcher with the head elevated on three pillows, the intrathecal space was entered in the lumbar region and the pressure repeatedly

TABLE II

Effect of Coramine * on Circulatory Signs

Case	Diagnosis	Duration of Coramine Treatment	Art. Blood Pressure	B.C.T.	Pulse	V.C.	Diuresis	E.K.G.
5	Art. Scl.	14 days	Wide variations	39 sec. (31)	90 (100)	1000 c.c. (1400)	None	PR 0.24, QRS 0.12 Marked T changes (No change)
9	Art. Scl.	10 days	110/80 (110/80)	35 sec. (39)	76 (78)	1200 c.c. (1800)	None	Left B.B.B. (No change)
10	Luetic AI	12 days	155/55 (150/50)	30 sec. (25)	80 (80)	1400 c.c. (1200)	None	PR 0.22, QRS 1 and 2 low amplitude (PR 0.2, QRS 1 and 2 normal)
11	Rh.MS, MI	11 days	140/78 (140/76)	38 sec. (28)	80 (80)	1700 c.c. (1800)	None	Marked T changes (No change)
12	Art. Scl.	10 days	115/75 (110/72)	25 sec. (26)	90 (90)	1800 c.c. (1700)	None	Severe myocardial damage (No significant change)
13	Art. Scl.	9 days	180/110 (210/100)	26 sec. (40)	85 (90)	800 c.c. (1500)	Lost 7 lbs.	Marked T changes (No change)

* Dosage in each case was 3 c.c. p.o. 4 i.d.
(—) Indicates readings at end of treatment.
B.C.T. Blood circulation time (saccharin arm to tongue).
V.C. Vital capacity.

These cases receiving Coramine showed no significant change in blood pressure; the apparent changes in case 13 represent a fluctuation noted frequently in this patient during his hospitalization. The blood circulation time improved in three cases, was uninfluenced in one case, and became prolonged in two cases. Pulse rates were fairly constant, case 5 showing a slight increase. Although the vital capacity increased moderately in three cases there was little change in the others. Only one case showed evidence of weight loss. Electrocardiographic patterns remained nearly unchanged.

recorded until it showed no tendency to vary for at least 10 minutes. Accepting this as a basal level, 5 c.c. of Coramine were given intravenously over a period of 3 to 4 minutes and readings of the pressure recorded at short time intervals. Given in this manner, and the dose is admittedly large, Coramine caused most patients to complain within two or three minutes of the onset of the administration, of a sensation of burning heat over the body, followed by perspiration and restlessness. Burning and itching of the face, especially of the nose, were occasionally encountered. This picture in one patient (case 5) was attended with considerable excitement, and it is felt that these symptoms are due to widespread cerebral stimulation. No nausea nor palpitation was noted. In all cases there has been a resultant drop in intrathecal pressure, the maximum being reached in from 10 to 20 minutes. (Table 3.)

Four patients in this group (cases 16 and 5 (figures 1 and 2) and cases 17 and 24) showed an initial rise of intrathecal pressure, associated with

TABLE III

Effect of Coramine * on Intrathecal Pressure

Case Number	Diagnosis	Art. Blood Pressure	Intrathecal Pressure †	
			Before Coramine	After Coramine
4	Rheumatic AS, AI	170/65	225	190
5	Art. scl.	140/80	315 (245)	220 (200)
14	Luetic AI	160/60	190	132
15	Luetic AI	184/70	275 (245)	192 (175)
16	Art. scl. hypertension	230/140	435	370
17	Art. scl. hypertension	170/95	140	118
24	Art. scl. hypertension	144/102	225	180

* Dosage—5 c.c. intravenously.
† Intrathecal pressure in mm. spinal fluid.
(—) Indicates readings during quiet phase of cyclic breathing.

Each case showed an initial elevation of the intrathecal pressure. Fall in pressure to lowest figure occurred between 10 to 20 minutes after 5 c.c. of Coramine intravenously. The figures in parentheses (—) indicate an alternative reading taken during the quiet phases in two patients with periodic breathing. Case 5 is illustrated graphically (figure 2).

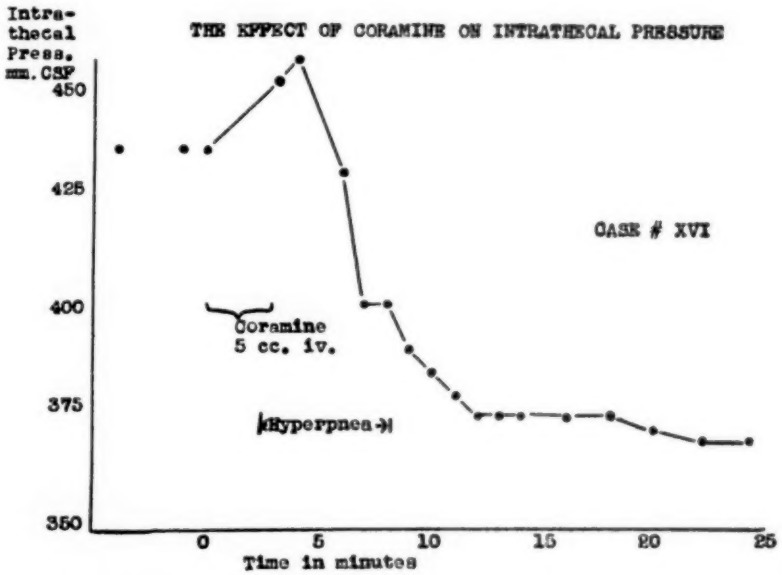

FIG. 1. Case 16: The initial basal intrathecal pressure was 435 mm. of spinal fluid. Coramine (5 c.c.) intravenously given over a period of 3 minutes caused a temporary rise in pressure concomitant with the onset of hyperpnea and a slight sensation to the patient of burning of the face lasting a few minutes. Pressure then fell sharply to 375 mm.

hyperpnea, "burning" sensation and excitement, which preceded a fall in pressure. Two cases (4 and 15), with slight immediate symptoms, showed a prompt drop, while the remaining case with moderate reaction to Coramine maintained an unchanged pressure for five minutes from the onset of injection before a fall was noted. Two patients (case 5 (figure 2) and case 15) with marked Cheyne-Stokes respiration gave two readings—one during

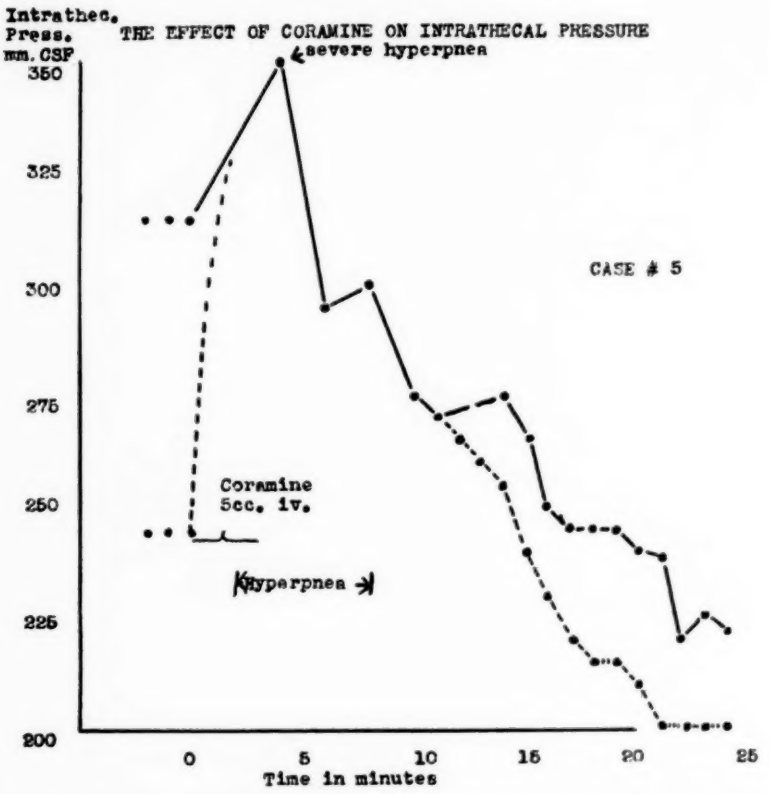

FIG. 2. Case 5: The initial basal intrathecal pressure in this patient with Cheyne-Stokes respirations is 315 mm. of spinal fluid during the hyperpneic phase and 245 mm. during apnea. Coramine (5 c.c.) intravenously, given over a period of three minutes, caused a sharp increase in pressure, along with abolishment of periodic breathing and attended with marked excitement, severe hyperpnea, burning sensation and free perspiration for a few minutes. The pressure then fell sharply. After 12 minutes respirations again began to alternate between quiet (interrupted lines) and exaggerated (solid lines) phases, although there were no periods of apnea for one hour.

apnea and the other during hyperpnea. Periodic breathing in these cases was replaced, during or just after the administration of Coramine, by regular hyperpneic respirations, but 5 to 12 minutes later there was a cyclic variation between quiet and exaggerated phases without periods of apnea.

In spite of the tendency to return to Cheyne-Stokes breathing (figure 2) as evidenced by an alternation between quiet and exaggerated phases, the

pressure continues to fall, suggesting little correlation between the fall of pressure and the type of breathing. Two cases with Cheyne-Stokes breathing that responded in this manner to Coramine, failed to be relieved of their periodic breathing by withdrawal of large amounts of cerebral spinal fluid with considerable reduction of pressure.

Effect on Venous Pressure

Venous pressure determinations have been made on seven subjects using the apparatus described by Moritz and von Tabora [18] for continuous readings. Because of orthopnea the patients' heads were elevated 30 degrees above the horizontal; the arms were abducted to 45 degrees and supported in a comfortable position. There was no effort to be exact with the reference point for zero readings, although this point was roughly estimated.[19] Readings were repeatedly made until there was no variation for 10 minutes and then Coramine was given intravenously in doses of 5 c.c. over a period of 3 minutes. (Table 4).

Table IV

Effect of Coramine * on Venous Pressure

Case Number	Diagnosis	Art. Blood Pressure	Venous Pressure †	
			Before Coramine	After Coramine
5	Art. Scl.	140/80	205	156
18	Art. Scl.	136/80	214	185
19	Luetic AI	165/50	94	Same
20	Luetic Aortitis	140/80	170	145
21	Art. Scl.	110/90	380 (345)‡	340 (323)‡
22[1]	Art. Scl.	195/115	164	Same
23	Art. Scl.	230/145	142	115

* Dosage—5 c.c. intravenously.
† Venous pressure in mm. sodium citrate.
‡ Readings during quiet phase of respirations.
[1] Cheyne-Stokes. Respiratory rate 9–10 min., azotemia.

Following the intravenous use of Coramine (5 c.c.) there has been a fall in venous pressure in five of the seven cases, the maximum fall reached within 20 minutes. In two cases (19 and 22) there was no appreciable change. Case 22 died two days later with renal insufficiency. Case 21, with periodic breathing, is graphically illustrated (figure 3).

It is noted that two patients (cases 19 and 22) showed no change in pressure. One of these cases (19) had a normal venous pressure, while the other (22) had Cheyne-Stokes respirations, with a rate of 9 to 10 per minute, marked azotemia, and died two days later of renal insufficiency. This patient's respirations were not altered in rate or depth. The remaining cases did respond with a fall in pressure reaching the minimum level within

20 minutes, although the degree of fall was not marked. Figure 3 graphically represents the response in a patient with Cheyne-Stokes respirations (compare with figure 2).

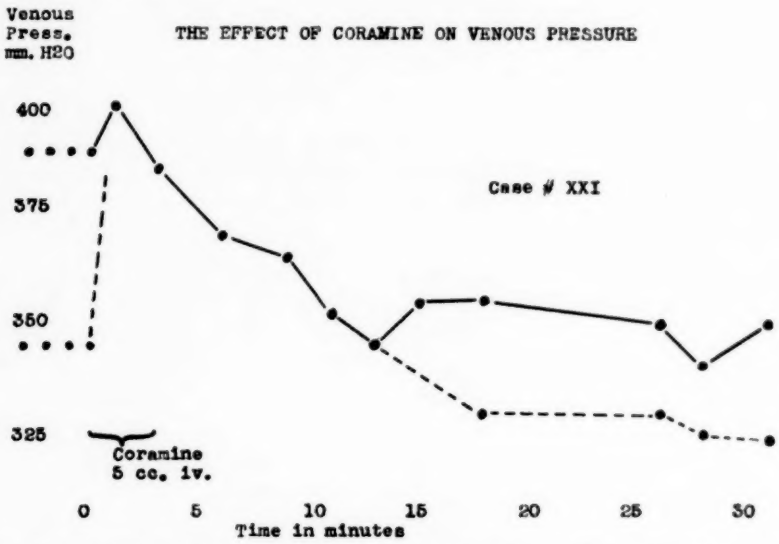

FIG. 3. The initial basal venous pressure in this patient with Cheyne-Stokes respirations is 390 mm. sodium citrate during the hyperpneic phase and 345 mm. during apnea. Coramine (5 c.c. i.v.) quickly abolished periodic breathing and the pressure gradually fell. After 13 minutes respirations again began to alternate between quiet (interrupted lines) and exaggerated (solid lines) phases, although there were no periods of apnea during the experiment.

ABSTRACT OF CASES TREATED FOR RESPIRATORY DISEASES

Case 1. W. W., colored male, aged 64, a known cardiac with arteriosclerotic hypertensive cardiovascular disease, admitted Dec. 22, 1938 with dyspnea, orthopnea, cough, edema and epigastric discomfort. Considerable improvement followed routine treatment, but nocturnal dyspnea recurring 7 to 11 times each night remained a distressing symptom and was only fairly well controlled with opiates. We first saw him on Jan. 29, 1939, and found him to have moderate dyspnea and orthopnea, with slight engorgement of the neck veins. Heart rate 64, rhythm irregular with frequent premature contractions, cardiac enlargement, mitral insufficiency, blood pressure 210/100 with pulsus alternans. Few râles at lung bases. Liver down 4 cm. and slightly tender. Slight sacral edema. Digitalis gr. iss continued as before and Coramine 3 c.c. per os five times daily, started. During the first 48 hours there was little change except for the patient's statement that the attacks were much less severe. During the next two days attacks recurred only four and three times at night, dyspnea was much less marked, appetite improved and the patient said he felt much better. Inadvertently no Coramine was given for the next three days and symptoms recurred, the number of attacks of paroxysmal nocturnal dyspnea increased to 7, 8, and 14 on successive nights, dyspnea became constant and appetite failed. Upon returning to Coramine 3 c.c. five times daily for the next 10 days (Feb. 8–17 incl.) attacks diminished on successive nights to 8, 8, 8, 4, 0, 0, 0, 0, 0, 0, while relief of disturbing dyspnea and return of appetite were more prompt. The patient was allowed out of bed on Feb. 14 and left the hospital on Feb. 20, symptomatically recovered.

Case 2. J. A., colored male, aged 60, entered the hospital on Feb. 10, 1939 complaining of substernal pain radiating to the neck and left arm, increased with exertion. Attacks lasting 5 to 10 minutes have been more severe and frequent in the past six weeks. Had shown progressive evidence of myocardial failure. On admission he was found to have cardiac disease, arteriosclerotic and hypertensive, enlargement, premature beats, mitral insufficiency, class 4, this picture being complicated by cardiac psychosis, and questionable presence from history and electrocardiogram of anterior myocardial infarction (proved at necropsy). Digitalization started slowly. On the second day following admission (Feb. 12) Cheyne-Stokes respirations appeared irregularly, patient was more confused and temperature rose due to broncho-pneumonia. On Feb. 13 Cheyne-Stokes respirations were constant. On Feb. 16 Coramine 2 c.c. given intravenously and a 5 c.c. dose intramuscularly, the latter being repeated every four hours. After the third dose respirations became regular and the patient slept. He remained confused but passed a more restful night. On Feb. 17 it was observed that each dose of Coramine would control the respirations for periods of ¾ to 2 hours after each injection; the remainder of the time they were of the Cheyne-Stokes type. On Feb. 18 and Feb. 19 no periods of Cheyne-Stokes were observed and the medication was then stopped. Cheyne-Stokes did not recur on Feb. 20 but the patient died suddenly on that day.

Case 3. W. S., colored male, aged 69, a known arteriosclerotic hypertensive cardiac with cardiac enlargement, mitral insufficiency, gallop rhythm and periods of paroxysmal (nodal) tachycardia, class 4, Wassermann positive. Entered on Jan. 29 with marked dyspnea and Cheyne-Stokes type respirations. Blood pressure 180/100. Vessels markedly sclerotic. Neck veins engorged, free fluid in right pleural cavity, 2 plus sacral edema, abdomen distended. Started on Coramine on Jan. 30, 3 c.c. p.o. five times daily. On Feb. 6, Cheyne-Stokes was replaced by regular breathing and dyspnea less marked. However, the patient became more confused mentally. The day following he reverted to Cheyne-Stokes in spite of continued medication. On Feb. 8, the oral dose was replaced by 3 c.c. i.m. five times and this was continued through Feb. 11 without significant benefit. After an additional 2½ weeks in bed Cheyne-Stokes and sensorium cleared and the patient made a complete symptomatic recovery. It is worthy of note that for most of the course with Cheyne-Stokes respirations, orthopnea was not a marked feature, the patient lying flat in bed without apparent added discomfort.

Case 4. F. S., white male, aged 42, known rheumatic fever in early teens, and definite evidence of rheumatic heart disease, cardiac enlargement, aortic stenosis, aortic insufficiency, and mitral insufficiency. Decompensation caused by severe respiratory infection and cough. When admitted Feb. 16, there was evidence of failure in engorgement of neck veins, râles at lung bases, marked precordial protodiastolic gallop, liver 2 cm. below costal margin and slight ankle edema. His presenting symptom was paroxysmal dyspnea, almost entirely preventing sleep for the past few nights. Digitalization started on admission, and the first night the patient rested after the use of morphine sulphate subcutaneously. Feb. 17 pentobarbital failed to give relief of frequent attacks. Feb. 18 it was noted that Cheyne-Stokes respirations occurred when patient was relaxed. At 7:30 p.m. and again at 10:00 p.m. Coramine 5 c.c. was given intramuscularly and the patient slept through the night without evidence of Cheyne-Stokes or dyspnea. On Feb. 19 in the afternoon, paroxysmal attacks recurred and respirations rhythmically alternated between a quiet and exaggerated phase. Five c.c. of Coramine were given intravenously with rhythm becoming regular and no tendency to Cheyne-Stokes. This dose was repeated intramuscularly four hours later and the patient again had a good night. No further respiratory embarrassment was experienced during his stay in the hospital.

Case 5. Wm. Sh., colored male, aged 60, has been followed in our clinics since

1934 because of arteriosclerotic hypertensive heart disease, and positive Wassermann. Admitted to the hospital 10 times because of decompensation. On admission Sept. 7, 1938, patient was decompensated, with marked orthopnea and dyspnea, gallop rhythm, venous engorgement, and an electrocardiogram that showed a left bundle branch block, first degree heart block (PR 0.22 sec.) and premature ventricular contractions. Blood pressure 130/80 with pulsus alternans. Improvement was noted until Oct. 1 when gallop rhythm became more marked and he complained of frequent attacks of paroxysmal dyspnea, particularly during the late afternoon and night. On Oct. 4 Coramine 3 c.c. four times a day was started p.o. Less frequent attacks occurred on the fifth, and on the sixth dyspnea had been relieved and his general condition improved so that he was allowed out of bed on the twelfth. Coramine stopped on the nineteenth when the patient was discharged.

Readmitted on Nov. 15 with Cheyne-Stokes respirations and cardiac psychosis. Gradual general improvement noted although Cheyne-Stokes persisted. Coramine 3 c.c. p.o. four times a day given between Dec. 13 and Jan. 4, 1939 failed to improve respiratory distress. Improvement continued, however, so that he left the hospital on Feb. 2.

Feb. 9 in O.P.D. again in failure with marked Cheyne-Stokes respirations, gallop rhythm, and irregular pulse due to auricular, nodal and occasional ventricular premature contractions. Coramine was given in teaspoonful doses four times daily. At the next O.P.D. visit one week later (Feb. 16) there was no evidence of Cheyne-Stokes although dyspnea was still marked, and there was no return toward compensation. Symptomatically the patient stated that he had obtained definite relief of marked respiratory distress about 24 hours after starting this medication. A week later (Feb. 23), having continued the same dose of Coramine, the patient presented himself with evidence of increased edema, but dyspnea was only minimal and gallop rhythm had disappeared. Between Feb. 23 and March 9 Coramine in drachm doses was taken three times a day, but decompensation was marked, Cheyne-Stokes again present, dyspnea marked and coupled rhythm present (from digitalis toxicity).

Admitted March 9 and intrathecal pressure recorded as noted in figure 2. Five c.c. of Coramine intravenously converted Cheyne-Stokes to regular hyperpneic rhythm for about 10 minutes, followed by cyclic breathing, but no periods of apnea for one hour.

On March 15 as coupling had not been observed for three days, and because patient showed signs of increased failure and periodic breathing continued, digitalis gr. 1½ daily and Coramine 4 c.c. p.o. five times a day were started simultaneously. On March 16 respiratory rhythm was again regular. Coramine was stopped on March 20 and patient returned to periodic breathing on March 23. Relief of congestive failure followed the later use of intravenous mercurial diuretics, and was not influenced by Coramine.

Case 6. S. N., aged 68, white female, with hypertensive arteriosclerotic cardiovascular disease had been considerably incapacitated for over a year. Electrocardiograms showed left bundle branch block. On three separate occasions during a nine month period of follow, she had periodic breathing and each time responded to 25 drop doses of Coramine p.o. four times a day, improvement and cessation of Cheyne-Stokes occurring within 24 to 48 hours. During the last two months of follow she continued taking Coramine in 25 drop doses three times a day regularly without return to abnormal respiratory rhythm.

Case 7. G. M., colored male, aged 53, admitted March 3, 1939, having had progressive signs and symptoms for three months, viz: epigastric discomfort, dyspnea, and palpitation on exertion; edema noted especially in the past week and during this time he has had hallucinations, delusion and excitability. On admission patient showed evidence of cardiac disease, arteriosclerotic, hypertensive, enlargement, gallop

rhythm, class 4. Cardiac psychosis and moderately marked systemic, portal and pulmonary congestion present. Breathing was of the periodic type and orthopnea was marked. He had been taking digitalis prior to admission; this was increased and continued. Coramine 4 c.c. intramuscularly was started on the day following (patient refused everything by mouth) but lacking coöperation it was given irregularly and stopped on March 7, periodic breathing persisting. Over a period of three weeks the patient made gradual improvement, but on March 31 dyspnea became more marked and he again became confused. Cheyne-Stokes reappeared on Apr. 2 and this was more marked on April 5. On that day 5 c.c. of Coramine were given slowly intravenously, and Cheyne-Stokes breathing immediately replaced by hyperpneic regular breathing for about 5 minutes, following which breathing alternated between quiet and exaggerated phases. Periods of apnea were observed ½ hour later. Then Coramine 3 c.c. p.o. was started every three hours. The next day (April 6) there was no apparent change. An April 7, for variable periods following medication, respirations were regular and the patient stated that he was breathing easier. On April 8 respirations remained regular and there was no evident dyspnea. Breathing was easy and regular on April 9 and April 10. On April 10 Coramine was discontinued and two days later on April 12 Cheyne-Stokes breathing was again distressing. At noon on April 12 Coramine was resumed as before. Breathing again became regular on the afternoon of April 13 and was attended with symptomatic relief.

Case 8. T. F., aged 57, white male, admitted to the hospital Nov. 10 because of attacks of nocturnal dyspnea and cardiac asthma recurring with increasing frequency and severity for the past two months. On examination he was orthopneic, dyspneic, somewhat cyanotic with pulmonary emphysema and râles at the lung bases. Cardiac enlargement with diminished heart sounds and apical systolic murmur was noted. Blood pressure 200/114. Peripheral vessels markedly sclerotic and tortuous. Liver down 3 cm. No peripheral edema. Oxygen and narcotics gave some relief but did not prevent attacks. Coramine medication was started on Nov. 14 after four days of the above treatment, and the drug was given in doses of 4 c.c. five times daily. There was gradual improvement progressing to complete relief in three days. Slight nausea was noted after each dose of Coramine. On Nov. 18 this medication was discontinued and attacks of paroxysmal dyspnea returned two days later (Nov. 20). Coramine again given this time in 3 c.c. doses 5 times daily with relief within 15 hours. On Dec. 3 medication again stopped, and on Dec. 4 symptoms reappeared, but were quickly relieved by further medication.

Case 25. J. Q., a 69-year old male carpenter, with arteriosclerotic heart disease who suffered a myocardial infarction in the spring of 1939. Admitted Dec. 1939 because of heart failure and paroxysmal nocturnal dyspnea. Had been digitalized and maintenance dose was continued. Improvement was progressive until Jan. 6, 1940 when he had a cerebral accident, following which failure increased. On Jan. 21, fever rose to 101° F. due to broncho-pneumonia. On Jan. 23 Cheyne-Stokes respirations were noted and two days later this was distressing with periods of apnea lasting 30 to 35 seconds. Coramine (4 c.c. per os) was then started and repeated 5 times daily. Within 24 hours respirations were converted to quiet normal breathing, even during sleep, and so this medication was stopped. Temperature now normal. Eight hours later Cheyne-Stokes reappeared and on Jan. 28 Coramine was again given as before, and on the twenty-ninth normal breathing was present. Because of hiccoughs and nausea the dose of Coramine was reduced to 3 c.c. five times daily with relief. Nausea recurred on Feb. 4 and treatment again was discontinued. Cheyne-Stokes again present on Feb. 6, but as this was not distressing, no further Coramine was used. Two days later (Feb. 8) respiration became normal and patient continued to improve without further treatment.

Case 26. J. E., a 74-year-old colored man, entered the hospital because of signs

of increased cardiac failure, severe dyspnea and mental confusion. Digitalis, which had previously been prescribed, had not been taken faithfully during the past several months. Arteriosclerosis of the peripheral vessels was extreme, there was no perceptible radial pulse and blood pressure readings could not be made. Cheyne-Stokes breathing was distressing with periods of apnea lasting 30 to 40 seconds. Electrocardiograms showed bundle branch block of the common type. Marked cardiac enlargement. Occasional premature beats and apical systolic murmur. Digitalis was given, and, on the third day of hospitalization, Coramine was started in 4 c.c. doses by mouth, repeated 5 times daily and continued for seven days. Although there was progressive clearing in the sensorium, Cheyne-Stokes breathing persisted, gradually lessening in severity. It was felt that Coramine had not afforded significant relief.

Comments

Believing from reports in the literature and from our experience, that direct action of Coramine on cardiac efficiency is not marked, we look to the respiratory system for an explanation of a favorable action on the respiratory distress of cardiac disease. It remains a matter of speculation whether such relief results from (1) stimulation of the respiratory center; (2) reduction of intrathecal pressure; (3) relief of cerebral venous engorgement; or from (4) some other unknown factor. The widely accepted theory for the cause of the type of Cheyne-Stokes respiration associated with cardiovascular disease assumes that with a failing circulation there develops a relative anoxemia of the cerebral tissue, the respiratory center becomes depressed and apnea results; carbon dioxide then increases and acts as a respiratory stimulant reinitiating respirations until the carbon dioxide content is sufficiently diminished so that the cycle repeats.

Coramine's ability to stimulate cerebral tissue has considerable support from the numerous studies on denarcotization. CoTui [20] gave lethal doses of procaine hydrochloride cisternally to dogs and with Coramine was able to reduce the mortality. By irrigating the fourth ventricle of one animal with procaine hydrochloride respirations were completely abolished, yet were restored with 10 c.c. of Coramine intravenously, given in two doses of 5 c.c. each. The sweating and restlessness, which we frequently observed after intravenous Coramine, suggest stimulation of nervous tissue, and the transient hyperpnea indicates stimulation of the respiratory center. However, Greene and Heeren [21] do not believe that aminophyllin, an agent which has been shown to control Cheyne-Stokes respirations, acts entirely as a respiratory center stimulant. Their opinion is based on their observations that carbon dioxide, a known central respiratory stimulant, does not convert Cheyne-Stokes to normal breathing but causes a prolongation of the hyperpneic phase (which we find to be so with single large intravenous doses of Coramine) while caffein 0.5 to 1 gram doses produces a Biot type of breathing. The failure of oxygen to benefit this type of abnormal breathing is of doubtful significance in view of experimental evidence that anoxemia gives a variable response as a respiratory stimulant.[22] Nathanson and Fitzgibbon [23] could not relieve Cheyne-Stokes breathing with the use of benze-

drene sulphate (10 mg. intravenously) nor with Coramine in 2 c.c. doses, although these are credited cerebral stimulants, while theophyllin proved of value. In their report, one of three cases was temporarily relieved with caffein sodio-benzoate in doses of 0.75 gram. With accumulating knowledge of the physiology of respirations [24] we know that receptors for reflex respiratory center stimulation are present (carotid sinus, arch of the aorta, alveoli, etc.) and that these may be affected by changes in the carbon dioxide content of the blood, by simple rise in pressure, acting as a physical stimulus,[22] by ischemia of the carotid body [22, 25] and by stimulation with chemical agents other than physiological agents.[26, 27, 28] Heymans, Bouchaert and Dautrebande [26] showed that cyanides, nicotine, lobeline, etc., act on these receptors to give a reflex hyperpnea and that in small doses these substances do not directly stimulate the respiratory center. Wright [27] confirmed these findings with a large group of respiratory stimulants, and he emphasizes that, although the peripheral receptors are the more sensitive to most of the agents, direct stimulation of the respiratory center can be accomplished by sufficient concentrations of the drugs. This has been shown to be the case with Coramine by Zunz and Tremonti [28] on animal preparations.

That changes in intrathecal or venous pressures may be of significance is suggested by the upright position assumed by patients with severe dyspnea. Harrison [16] had noted a relationship between cardiac failure and increase of intrathecal pressure, and observed a higher cisternal pressure in the recumbent than in the sitting posture and believed this to be the mechanism of orthopnea. Greene, Paul and Feller [17] found that theophyllin with ethylenediamine (aminophyllin) given intravenously produced a decline in the intrathecal and venous pressures, and that the improvement in dyspnea and conversion of Cheyne-Stokes respirations to a regular rhythm was related to the decline in pressures, suggesting that this might be the mechanism for relief. However, glucose in 50 per cent solution given in 50 to 200 c.c. injections, failed to relieve Cheyne-Stokes [21] although this procedure lowers the intrathecal pressure. We have observed that Coramine given intravenously in single doses of 5 c.c. only temporarily alters Cheyne-Stokes breathing, although a definite reduction of the intrathecal pressure is seen. Further, as review of figure 2 will show, there is a continued fall of pressure in spite of the recurrence of respirations alternating between quiet and exaggerated phases, indicating that the type of respiration has little relation to the change in pressure. Simple drainage of cerebral spinal fluid, to lower the intrathecal pressure, has failed to relieve periodic breathing in patients whose respirations are temporarily altered with intravenous Coramine.

Ernstene and Blumgart [29] noted an association between an elevated venous pressure and orthopnea and, in their opinion, this increased pressure causes an impairment of circulation to the respiratory center to produce orthopnea. Harrison et al.[30] demonstrated that elevation of venous pressure or intra-auricular pressure causes reflex stimulation of breathing, the reflex presumably arising in the heart or the great veins and the impulses carried by the

vagus nerves. That cerebral blood flow is subnormal in hyperpneic cardiac patients is supported by McMichael[31] from data on jugular vein oxygen content. There is little evidence from the present data that fall in venous pressure is striking enough to afford relief of cerebral engorgement or otherwise improve blood flow.

Summary and Conclusions

It has been demonstrated that Coramine may have a beneficial action on the abnormal respirations associated with cardiac disease. Dramatic responses, however, are not usually found from oral doses, but rather a slow progressive improvement—usually one to three days elapse before the optimum benefit is realized. A more prompt but transient response follows its use intravenously and may be attended (as used in 5 c.c. doses) by symptoms from widespread cerebral stimulation.

Cardiac efficiency was not shown to be constantly improved from prolonged oral use of Coramine.

Decline in intrathecal pressure, following its intravenous administration, was observed and, to a less constant or striking degree, a decline in venous pressure. That these pressure changes are directly related to the improvement noted is considered doubtful. The present evidence points to Coramine's stimulation, as a chemical agent, of the respiratory receptors, either peripherally or centrally.

Further studies are indicated.

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IRON METABOLISM AND ITS RELATIONSHIP TO ANEMIA AND THERAPY *

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Iron, in the form of an inorganic salt, may be considered as a specific remedy for certain types of anemia and will produce results which are comparable to those obtained by liver extract in the treatment of pernicious anemia. The use of iron as an antianemic remedy is not new but the results which have been obtained in recent years are more striking than in the past and have served to focus attention on this metal. The increased popularity and the apparent increased effectiveness have been due primarily to the administration of adequate amounts of iron to properly selected cases whereas in the past it has frequently been used indiscriminately in all types of "secondary" anemia. The renaissance has been due, therefore, to a better understanding of the pathogenesis of the anemias rather than to any increased effectiveness of the drug itself.

When an adequate amount of iron is not available for hemoglobin formation a hypochromic type of anemia develops which is characterized by microcytosis, hypochromia of the individual erythrocytes, and low color and volume indices. The cause of the deficiency in available iron varies from case to case, and although there are obvious gaps in our knowledge of iron absorption, storage, and utilization, certain facts have been established which serve to explain the pathogenesis of these anemias. Opinions differ as to the amount of iron which is required each day by a normal individual and many types of experiments have been carried out in an attempt to ascertain this level.† [1] Some observers believe that a diet containing 5 mg. of iron per day is sufficient to maintain a normal iron balance [2] while others believe that larger amounts are necessary. We have shown [1] that a daily iron intake of from 3.81 to 6.76 mg. resulted in a negative iron balance in five individuals whereas when four of these same subjects were given diets containing from 12.22 to 15.53 mg. of iron all were in positive balance. From these results and from further studies on a group of 42 patients it was concluded that the dietary iron intake should be in the neighborhood of 12 to 15 mg. per day to insure adequate iron absorption. It has been shown that not all of the iron which is present in various foods is available for absorption and utilization [3, 4, 5] and this may be taken as another point in favor of the higher dietary iron intake.

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† A complete survey of the literature on the subject of iron requirements is given in reference [1].

The acidity of the gastric juice plays an important rôle in the absorption of iron from the gastrointestinal tract and achlorhydria appears to be a more important factor in producing an iron deficiency than does a low iron intake alone. The frequency with which an achlorhydria is found associated with hypochromic anemia has been repeatedly emphasized in clinical reports,[6, 7, 8, 9, 10] but in order to obtain more definite information on this feature iron balance studies were carried out on a group of patients.[11] In 11 patients with achlorhydria who received from 9 to 13 mg. of iron per day (average 10.86 mg.) there were 8 in negative balance and the average daily balance for the entire group was — 4.38 mg. In 15 patients with free hydrochloric acid in their gastric contents and with an average daily iron intake of 11.85 mg. there were only 5 in negative balance while 10 retained iron. The average daily retention for the 15 patients was + 1.02 mg. These results show that less iron is retained from the dietary iron intake when achlorhydria is present and it is obvious that under these circumstances the iron intake must be greater than in a person with a normal gastric acidity if an iron deficiency is to be prevented.

There are three primary factors which determine the iron requirement of an individual: the loss of hemoglobin iron by hemorrhage, the elimination of non-hemoglobin iron, and the formation of new iron containing tissue. The loss of iron through hemorrhage from any source will obviously require replacement and if the hemorrhage is continued over a long period of time the available supply of iron in the tissues of the body will become depleted and an iron deficiency will result. The loss of iron during normal menstruation must be taken into consideration in this connection and in determinations on 100 normal women the average loss was found to be 19.54 mg. of iron per period [12] while in a group of patients with frank menorrhagia the loss was found to be as high as 220.15 mg. per period.[13]

A second factor influencing the iron requirement is the elimination of non-hemoglobin iron. It is known that most of the iron is excreted through the gastrointestinal tract but determinations of the iron content of the feces fail to distinguish between that portion which has passed through the intestinal tract unabsorbed and unchanged and that which has been absorbed and reëxcreted into the bowel. The amount of iron excreted in the urine is small and in some balance studies has been ignored entirely. In an attempt to amplify our knowledge on this phase of iron metabolism the urinary iron output in 200 patients, equally divided between males and females, was studied.[14] The excretion varied from 0.08 to 1.63 mg. per day with a normal dietary iron intake and bore no constant relationship to the amount of iron ingested since the administration of large amounts of a soluble iron salt did not significantly alter the amount of iron excreted by this route. Although the amount varied from patient to patient it was quite constant in the same individual even at widely separated intervals. The iron excreted in the urine must represent iron which has been absorbed and, if not utilized, at least has been available for use and these results indicate that the amount

metabolized by the body is quite constant and does not vary significantly under ordinary circumstances.

The third factor influencing the iron requirement is the formation of new iron-containing tissue. This feature is important in the mother during pregnancy since the fetus at the time of birth contains in the neighborhood of 350 mg. of iron,[15] all of which must have been obtained from the maternal organism. It is obvious that the iron intake of the mother must be adequate, and the absorption efficient, in order to supply the fetal requirements. Not infrequently the maternal iron supplies are significantly depleted at this time. A large amount of iron is needed by an infant during the period of rapid growth and unless the iron reserves at birth are adequate to meet these demands an iron deficiency will result since the iron intake is low during this period. The demand for iron continues high during childhood [16] but is particularly great at the time of puberty and it has been estimated that the need for iron is as great at that period as during pregnancy.[17]

With these features of iron metabolism in mind we may examine the common types of hypochromic, iron deficiency anemias. The hypochromic anemia of infancy is particularly common in premature infants in whom growth is rapid, the demand for iron is great, and the iron stores not as large as normal. It is also common in the case of twin pregnancies. Such an anemia may also develop in normal children who have an adequate iron reserve at birth but whose diet is low in its iron content, as is the case with the prolonged use of cow's milk without supplementary foods. A nutritional anemia in adults may result from a long-continued low iron diet which results in a depletion of the iron reserves but in our experience such anemias are not severe, as a rule, unless there is an associated achlorhydria to further interfere with iron absorption. Classical cases of chlorosis are seldom encountered today although mild hypochromic anemias are common during adolescence. These are apparently due to the excessive demand for iron at this time, the onset of menses and in many cases a diet low in iron-containing foods.

The anemia of chronic hemorrhage results from the loss of iron at a more rapid rate than it can be replaced from the dietary intake. This ultimately results in a depletion of the iron stores and a reduction in the rate of hemoglobin regeneration. The hypochromic anemia of pregnancy is a result of several factors.[18] The fetal demand for iron is a severe drain on the maternal stores and is one of the essential features, but not all pregnant women develop this type of anemia so that some additional cause must be found. The diet may be inadequate in its iron content either through the patient's inability to procure proper food or because of persistent nausea and vomiting or a somewhat abnormal appetite. Of greater importance is the achlorhydria or hypochlorhydria which is present in practically all of these cases and prevents the absorption of sufficient iron to supply the demands.

Idiopathic hypochromic anemia occasionally has its onset during pregnancy or follows repeated pregnancies in patients who are unable to make up

the iron deficit incurred during that time. A low iron intake occasionally plays a part but is not a factor in all cases. Achlorhydria or hypochlorhydria is a constant finding and by interfering with the absorption of iron is an essential etiological feature. The primary factor in most cases, however, is the loss of iron through profuse menstruation. This excessive blood loss is not usually recognized by the patient so that no evidence of this is obtained from the patient's history. Determinations of the amount of hemoglobin and iron lost by this route in these patients have shown it to be excessive and in only two of the cases studied was the iron retention from the food large enough to compensate for the menstrual loss.[19] Idiopathic hypochromic anemia is essentially, therefore, a chronic hemorrhagic anemia in a patient in whom achlorhydria prevents the absorption of sufficient iron from the diet to replace that which is being lost.

From this analysis of the causative factors in various types of hypochromic anemia the rationale of iron therapy is evident and the reason for the excellent clinical results is obvious. There are, however, many features concerning the mode of action and the storage of iron which are unanswered. It is known that the administration of adequate amounts of various inorganic iron salts is effective in the treatment of these anemias.[20] The commonly recommended dose of these salts is large, as is shown for a few of the most widely used preparations in chart 1. It is recognized that the soluble salts

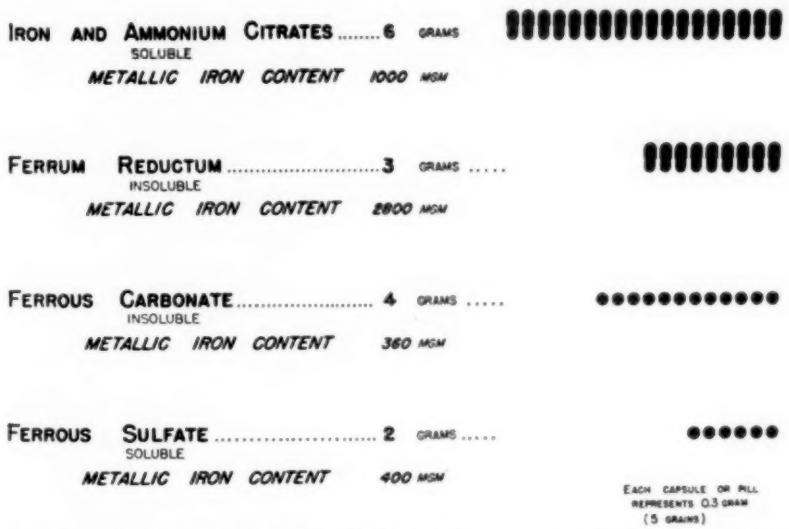

CHART I. Common iron preparations, usual daily dosage. Smaller doses of these drugs will produce a satisfactory hemoglobin response in many patients.

of iron are more readily absorbed and consequently are more effective than insoluble salts when compared on the basis of their elemental iron content. It is also apparent that ferrous are more effective than ferric salts when comparison is made on this basis and their greater effectiveness does not seem to

depend wholly on their solubility. Moore [21] has demonstrated an increase in the serum iron after the oral administration of an iron salt and the serum iron curve is higher after a ferrous than after a ferric salt. When a reducing agent is given with a ferric salt, however, the serum iron is increased to the same height obtained with a ferrous salt. His results suggest that iron is absorbed largely, if not entirely, in its ferrous form.

Since the iron content of the usual dose of an inorganic salt is much greater than can be accounted for by the iron used in new formed hemoglobin there is no adequate explanation for the greater effectiveness of massive doses as compared to smaller amounts. For this reason balance studies were carried out in an attempt to ascertain the fate of the ingested iron with various doses of an inorganic iron salt.

Iron and ammonium citrates, 3 grams per day yielding approximately 500 mg. of elemental iron, was administered to a group of patients with hypochromic anemia [22] and it was found that 67.4 per cent of the iron was excreted and 32.6 per cent was retained by the body (chart 2). Only 2 per

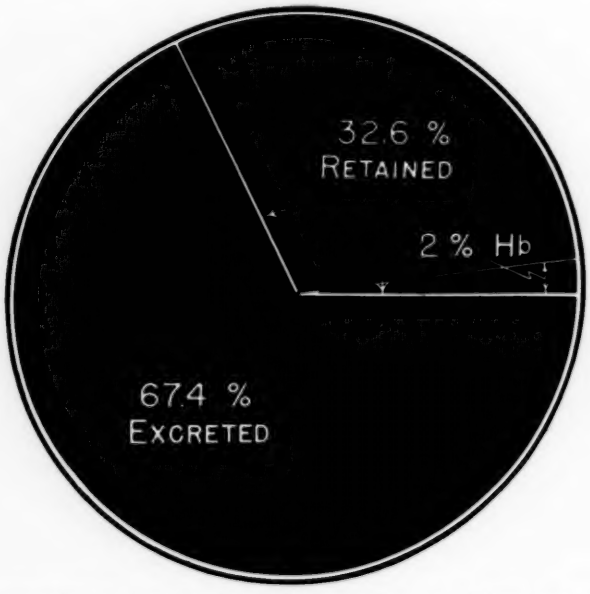

CHART II. Retention and utilization of iron. 500 mg. of iron per day as iron and ammonium citrates (3 grams). A very large amount of iron is retained.
Daily iron intake: 514 mg.
Excreted: 364.4 mg.—67.4%.
Retained: 167.5 mg.—32.6%.
Utilized as hemoglobin: 10.3 mg.—2%.
Average values from 10 cases.

cent of the ingested iron was used immediately in hemoglobin formation and no correlation was found between the amount of iron retained and the amount of hemoglobin regenerated. Exceedingly large amounts of iron continued to be retained with prolonged administration of the drug and if

the analogy can be drawn from animal experimentation, this iron was stored in the liver, spleen, and reticulo-endothelial system. Brock and Hunter [23] and Reimann [24] have likewise demonstrated a large retention of iron. These results do not substantiate the idea that absorbed iron is used quantitatively in hemoglobin formation nor that the amount of iron absorbed can be calculated from the amount of hemoglobin formed.

Further balance studies were carried out with smaller amounts of iron and ammonium citrates (1 gram per day yielding approximately 170 mg. of elemental iron) and the percentage of retention and excretion were similar to those with the larger dose.[25] In these patients 70 per cent was excreted and 30 per cent retained but 9.3 per cent of the administered iron was used immediately in hemoglobin formation (chart 3).

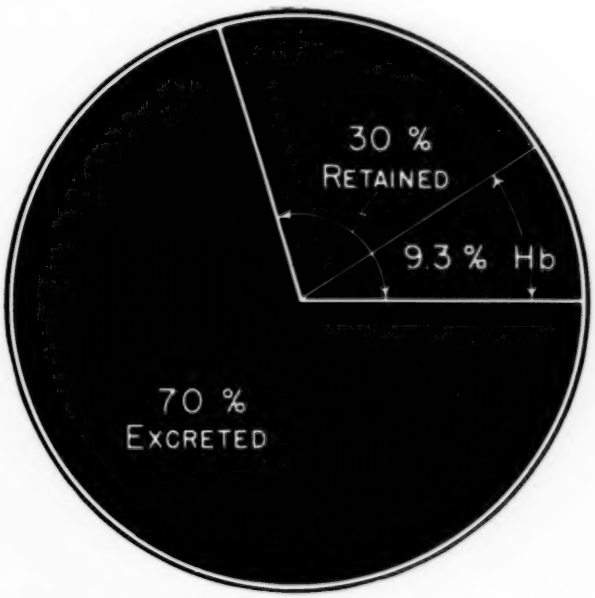

CHART III. Retention and utilization of iron. 170 mg. of iron per day as iron and ammonium citrates (1 gram). A large amount of iron is retained even with this small dosage.

Daily iron intake: 179 mg.
Excreted: 125.3 mg.—70%.
Retained: 53.7 mg.—30%.
Utilized as hemoglobin: 16.6 mg.—9.3%.
Average values from 6 cases.

When a liver fraction was added to the iron and ammonium citrates there was no significant alteration in the amount of iron retained nor in the rapidity of hemoglobin formation. With the addition of copper there was a decreased iron retention when small amounts of iron and ammonium citrates were given but the copper had no effect on larger doses of iron. In neither instance was the rate of hemoglobin formation significantly affected.[26] Although an achlorhydria was shown to diminish the retention of dietary

iron, it had no effect on the retention of iron from iron and ammonium citrates.[11] Iron and ammonium citrates were administered intramuscularly to a small group of patients and although the iron was retained there was no significant hemoglobin response although subsequent oral administration of iron produced a satisfactory response in two of the patients.[27]

It is to be noted in chart 3 that even when small doses of iron and ammonium citrates were administered there was a daily iron retention of 53.7 mg. and of this, only 16.6 mg. were used in hemoglobin formation. This produced a daily hemoglobin gain of 0.1, 0.15, and 0.08 grams per 100 c.c. of blood in three of the patients and this may be considered as a satisfactory response even though it is not as rapid as the optimum response obtained by Heath with larger doses.[28] The amount of iron retained from this dosage is far in excess of the amount used in hemoglobin formation and would seem to furnish enough iron not only for a satisfactory hemoglobin increase, but also an additional amount to replenish the depleted stores. We have used correspondingly small amounts of several iron salts and the results on hemoglobin regeneration are shown in chart 4. The results with iron and am-

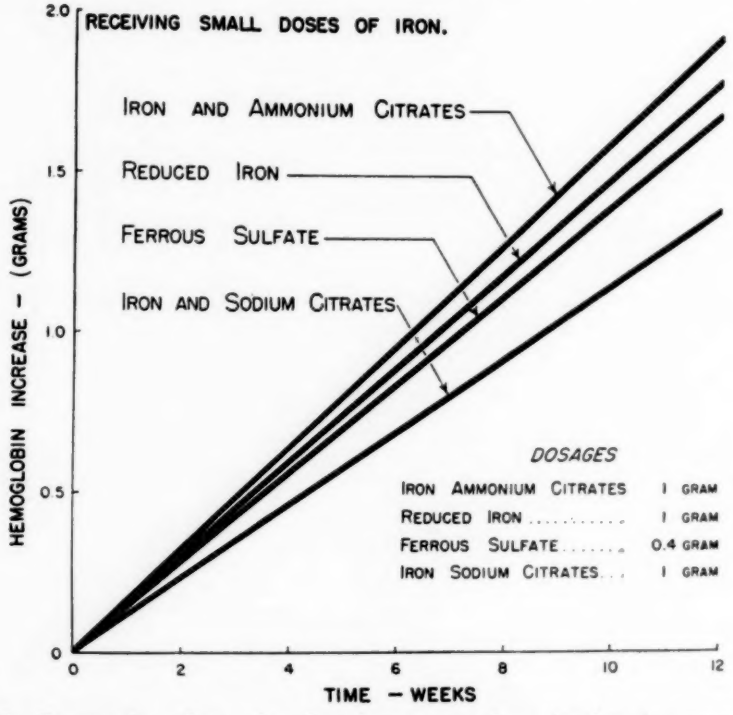

CHART IV. Comparative effects of various iron preparations showing the average hemoglobin increase for four groups of patients with mild anemia receiving small doses of iron.

monium citrates were obtained on 11 patients with an average initial hemoglobin of 11.3 grams. For the other drugs, there were six cases that received *Ferrum reductum* with an initial hemoglobin of 11.1 grams, seven

cases on *Ferri sulfas* with 9.8 grams of hemoglobin at the onset of therapy and eight cases receiving *Ferri et ammonii citras* with an average initial blood hemoglobin of 10.1 gm. The chart shows the hemoglobin increase that resulted from this therapy in a 12-week period. While these are not as rapid as may be obtained with large amounts of iron, they represent a fairly satisfactory hemoglobin increase.

It is known that the same amount of iron is not equally effective in all patients so that a dose which is adequate in one may not be sufficient for another.[28, 29] Our results show, however, that a satisfactory hemoglobin response can be obtained in most instances with considerably smaller amounts of iron than are generally employed but they cannot be interpreted as indicating that large amounts are never advisable. The mechanism by which an excessive amount of iron produces a more rapid response than does an adequate amount has not been satisfactorily explained. Brock [30] has shown that " excess " iron is more effective than " enough " iron and Whipple [31] has asserted that the excess iron exerts a " salt " or catalytic effect. We have demonstrated that a larger amount of iron is retained with a greater intake and Moore [21] has shown that the serum iron rises higher with larger doses of an iron salt. Since hemoglobin is formed more rapidly when these large amounts of iron are available, even though only a small part of this available iron is utilized, it suggests that the rapid increase is due either to a greater ease of synthesis when excessive amounts of iron are present or that iron does not act entirely as a form of replacement therapy but has an additional stimulatory effect on hemoglobin formation. The results indicate, however, that it is not necessary to administer excessive amounts of iron in all cases of hypochromic anemia.

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BRONCHOSTENOSIS COMPLICATING ALLERGIC AND INFECTIOUS ASTHMA *

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Bronchostenosis is a much more common complication of either allergic or infectious asthma than is generally believed. By bronchostenosis is meant a definite, localized, stricture-like narrowing of a bronchus. The lesion is felt to be primarily inflammatory in nature, and not referable to allergic edema or bronchial spasm. Two outstanding disturbances of function result when a bronchus becomes stenosed; first, the movement of air entering or leaving the segment of pulmonary tissue beyond the region of the stenosis is inhibited, and second, bronchial secretions which usually are excessive in asthma, are retained below the stenotic region so that a region of partial or complete atelectasis results.

During the past few years, a group of 140 patients suffering from asthma were specially selected for bronchoscopy, among whom we observed and treated 60 patients who were found to have definite stenosis of one or more bronchi. A study of this latter group revealed the fact that bronchostenosis complicating asthma generally produces characteristic symptoms and frequently, physical and roentgenologic observations which indicate that the physician may be dealing with this syndrome.

One of the more prominent symptoms encountered is severe, persistent, and sometimes paroxysmal cough, which of course aggravates the asthma. Frequently it is difficult or impossible, particularly at first, for the patient to raise sputum even by the most severe coughing. Later, the sputum appears, and it may become profuse. It is usually mucopurulent in character and in 40 per cent of the cases the sputum is at some time streaked with blood. The severe coughing is apparently caused by the patient's attempt to raise secretions retained by the stenotic region and later, when the stenosis recedes, either spontaneously or as a result of bronchoscopic dilatation, the retained secretions of a purulent or mucopurulent character are more easily raised. The source of the blood-tinged sputum is felt to be the seat of the bronchial inflammation and secondary pulmonary congestion which is present.

A second and very important symptom of bronchostenosis is fever. Febrile episodes, either with or without preceding chills, occurred in 68 per cent of the cases. The fever usually was of moderate severity and lasted from a few to many days. As the fever subsided, it was common for the patient to feel remarkably better and for the sputum to increase in amount.

* Read before the meeting of the American College of Physicians, Cleveland, Ohio, April 5, 1940.

The fever may be explained as referable to the toxicity of the retained secretions and to the inflammation present. The patient's temperature may be only slightly elevated in the morning, but it may increase rapidly in the afternoon, usually to 101° F. to 103° F. (38.3° to 39.4° C.). A sustained fever in which the temperature rarely decreases to a point below 100° F. (37.7° C.) may be present for days in some cases. The fever is usually accompanied by a leukocytosis. It should be emphasized at this point that febrile episodes, hemoptysis or even purulent sputum do not accompany uncomplicated asthma. The presence or the history of any one or all of these features in an instance of asthma should immediately arouse a suspicion of the presence of bronchostenosis or some other organic complication.

It is noteworthy that 53 per cent of the patients in our series who had bronchostenosis gave a history of pneumonia, and 35 per cent reported a history of pleurisy. Bronchostenosis is not infrequently mistaken for bronchopneumonia because of the severe cough, fever, blood-tinged purulent sputum and also the physical observations of localized congestion referable to the atelectasis which results from the blocked bronchus. Roentgenograms of the thorax also may support the impression of bronchopneumonia and may show a region of pneumonitis or atelectasis. However, after the acute phase subsides, bronchoscopic examination reveals a stenosed bronchus, dilatation and aspiration of which usually relieve the complication promptly. It should be axiomatic, therefore, that a patient who has asthma and who experiences one attack or repeated attacks of "pneumonia" certainly must be suspected of having had stenosis of a bronchus until it has been proved otherwise. This is true of asthmatic children as well as of adults.

The physical signs which may accompany bronchostenosis are secondary to the atelectasis which is present and consist chiefly of suppression of breath sounds and fremitus over the affected region, noted when the affected side is compared with the unaffected side. Less frequently dullness to percussion may be found over the atelectatic region. Careful and repeated examinations of the thorax occasionally will show a definite if not a pronounced difference in physical observations between the involved region in one lung and the uninvolved region in the opposite lung. Persistent unilateral physical signs are of the utmost diagnostic significance because in instances of uncomplicated asthma the physical signs are equal in each lung. In our patients, the stenosed bronchus was always found in the lower half of the lung and most frequently in the apical branch of the lower lobe bronchus, although other branches of the lower lobe bronchus were also often involved. Hence, significant physical observations will most often be found in the lower and posterior portions of the thorax.

The roentgenologic observations most often encountered in instances of bronchostenosis which complicates asthma are usually those characteristic of atelectasis, or less frequently, bronchiectasis. Although the roentgenologic observations sometimes suggest bronchiectasis, the physician must not con-

fuse the syndrome of bronchostenosis complicating asthma with true bronchiectasis. Kirklin [1] has described the roentgenologic picture of atelectasis, which is the most suggestive observation in bronchostenosis, as a "gauze-like shadow which extends more or less fan-like from the hilum toward the periphery of the lung and is of such slight density that the bronchovascular markings can be seen through it. Often an elevation of the corresponding arch of the diaphragm is associated with it and the heart and mediastinal structures may be displaced toward the affected side."

It should be emphasized that in 43 per cent of our cases results of the roentgenogram of the thorax were essentially negative. In still other cases, although the roentgenologic results were not negative, the roentgenologic observations were not significant in so far as the bronchostenosis was concerned. Several factors contribute to the high incidence of negative findings in roentgenograms in instances of bronchostenosis. In many instances the episode of bronchostenosis is not prolonged sufficiently to result in changes visible roentgenologically. In certain cases the opaque shadow cast by the heart obscures the affected portion as seen in the routine anteroposterior roentgenogram. In other instances in which long-standing previous bronchitis has been present, rather dense peribronchial shadows may obscure the more faint roentgenologic signs of atelectasis.

Only a relatively small group of patients who have asthma need bronchoscopy, and we feel the most common indication for such instrumentation is the need for ruling out or confirming the presence of possible complicating bronchostenosis. When the patient's history or the physical or the roentgenologic observations suggest the possibility of bronchostenosis which complicates asthma, such patients should have the benefit of a bronchoscopic examination, and should a stenotic bronchus be visualized, it can be dilated and the retained secretions can be removed by aspiration at the same time. It is common to see thick, tenacious mucus in excess in the bronchi, and often mucopurulent secretion is found. If stenosis of a bronchus is present at the time of bronchoscopy, a purulent secretion also may occasionally be seen oozing from the narrowed lumen of the bronchus. When the stricture is dilated by means of dilating forceps, varying amounts of retained mucopurulent or purulent secretion are found and may be aspirated. When patients who have asthma and a history suggesting bronchostenosis undergo bronchoscopy in the interval after they have apparently recovered from the complication, visualization of the bronchi may reveal no stenotic bronchus at the time, although in such cases there are usually increased secretions or other evidence usually encountered in instances of chronic asthmatic bronchitis. In other similar instances, some degree of stenosis persists, even after the febrile reaction has subsided, and its presence seems to aggravate the patient's cough and asthma and may contribute to frequent febrile episodes. Therefore, when a patient suffering from asthma who gives a history suggesting that he may have had complicating bronchostenosis in the past

is not doing well, bronchoscopic examination should be strongly considered, since a stenotic bronchus may be the one remaining factor preventing his recovery.

In addition to bronchostenosis caused by localized inflammation such as has been described, the physician may encounter bronchostenosis referable to other causes, such as primary bronchial malignancy complicating allergic asthma, as was found in one of our 60 cases.[2] Although no instances of it were found in our series, the physician might also encounter stenosis of a bronchus or of bronchi caused by tuberculosis, or by ulceration of calcareous material from a lymph node of the hilus into a bronchus, producing the effect of stenosis, or of the presence of a foreign body, or both. In all such instances, a correct diagnosis is crucial and it depends upon bronchoscopic examination, supplemented in certain instances by examination of tissue by a pathologist who is familiar with examination of specimens of tissue obtained from bronchi.

Occasionally, more than one stenotic bronchus is found in the same patient. These may be found in the same lung, or one in each lung. We have similarly noted, in instances of recurrence of bronchostenosis, that stenosis may recur in the same bronchus, but that it may occur also in a different bronchus in the same lung, or it may occur in the opposite lung, and at bronchoscopy, moreover, the site of the original stenosis be found to be entirely clear. The prevention of recurrences of bronchostenosis apparently depends on the success the physician meets with in carrying out three procedures: first, avoidance of infections of the respiratory tract; second, postural drainage, and third, the treatment of the underlying causes of the patient's asthma. Almost every episode of bronchostenosis which complicates asthma may be traced to an acute infection of the upper or lower portion of the respiratory tract, chiefly the common cold. For the asthmatic person, a cold is many times an invitation to an episode of bronchostenosis. To avoid infections of the respiratory tract or "colds" (and thereby bronchostenosis), the patient should be advised (briefly): (1) to keep warm and dry, (2) to get plenty of rest and to avoid fatigue, (3) to avoid others who have colds, and (4) to take a stock catarrhal vaccine, this last being the least essential procedure of the group. Postural drainage is important in cases in which bronchial secretions are in excess. The physician should bear in mind the fact that in all instances in our series of cases bronchostenosis was always found in the lower half of the lung; in other words, the region to which excessive secretions gravitate. Postural drainage done at the patient's rising and before his retiring, or more often if necessary, will help to correct this stagnation of secretions that apparently contributes to the development of bronchostenosis. In many cases the raising of these secretions is materially aided by the administration of iodide preparations.

Bronchostenosis respects neither age nor sex. In our group the sexes were represented almost equally, 29 males and 31 females being affected.

The youngest patient was six years old, the eldest sixty-four. Seven patients were less than twenty years old; two were more than sixty. The intervening decades were represented by 10 to 15 cases each. Bronchostenosis may complicate asthma at any age.

The occurrence of allergy in our 60 cases was frequent and noteworthy. In half of the patients so affected the asthma had an allergic basis. Hay fever was experienced by ten individuals, and seven had a definite allergy to drugs. Other examples of allergy included vasomotor rhinitis, urticaria, angioneurotic edema, allergy to food and eczema. It should be emphasized again at this point that in the case of allergic asthma, just as in infectious asthma (asthmatic bronchitis), episodes of bronchostenosis were ushered in by intercurrent acute respiratory infections. Exposure to allergens did not bring about a single episode of bronchostenosis so far as we were able to determine.

The treatment of bronchostenosis, as has already been indicated, is achieved by dilatation of the stenosed bronchus by means of dilating forceps introduced through the bronchoscope. This procedure is immediately followed by aspiration of the retained secretions from the bronchus. The therapeutic instillation of preparations of radiopaque oil following aspiration has not added materially to the results obtained and has been largely discontinued. The immediate results, as measured by the relief of the patient, the subsidence of fever, the eventual reduction in amount and improvement in character of the sputum, the improvement in the course of the asthma, and in many cases, the immediate reversal of physical signs of bronchial obstruction, are excellent. As has already been stated, recurrences can and do ensue, but they can be prevented best by the patient's avoiding respiratory infections and his carrying out the other prophylactic measures already outlined.

Patients who have asthma are usually tolerant of careful bronchoscopy as done by an experienced bronchoscopist. It need hardly be mentioned that the sputum of all patients should be examined for tubercle bacilli before the examination, and the patients all should have had, previously, a complete general examination and in addition special examinations, such as an allergic survey, examinations of the nose and sinuses and roentgenologic studies of the thorax and sinuses. When an episode of bronchostenosis is obviously rather recent, and the fever is high, the acute process should be allowed to subside before bronchoscopy is carried out. Rarely do patients who have bronchostenosis object when bronchoscopy is advised; many patients sense the feeling that something unusual is interfering with their raising bronchial secretions which previously were relatively easy to raise, and are almost eager for the procedure to be done, and other patients have expressed wonder why no one had heretofore advised looking into their air passages to see if obstruction was present.

It is obvious, from the foregoing, that the recognition and correct treat-

ment of bronchostenosis which complicates asthma is dependent upon close coöperation between the internist and the bronchoscopist. If the internist fails to recognize the possibility of the presence of bronchostenosis in certain instances of asthma, and does not refer the patient for bronchoscopic examination, the true state of affairs will be entirely overlooked. If the bronchoscopist can examine these patients, the stenosed bronchus, if present, can be dilated and the retained secretions can be aspirated, with great benefit to the patient.

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PHARMACOLOGICAL TREATMENT IN SCHIZOPHRENIC PATIENTS *

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THE insulin treatment of schizophrenic patients is essentially a medical treatment. Yet, it challenges the medical man, as well as the physiopathologist and the pharmacologist with respect to the generally accepted notions on the dosage of insulin compatible with safety, and with respect to the tolerance of various individuals to excessive amounts of this drug. The challenge lies chiefly in the fact that the complications of the insulin treatment—the so-called hypoglycemic shock—much dreaded by the physiopathologist—has been raised by the psychopathologist to a therapeutic virtue. Furthermore, the new treatment, aside from its curative value, in using the old drug in a new and very unorthodox manner, opens up a hitherto unexplored field for investigations. These promise to contribute not only to psychiatry and psychopathology but also, and perhaps more, to the chapters on general metabolism, and more specifically carbohydrate metabolism, and to our knowledge on the pharmacodynamics of insulin.

The insulin treatment of schizophrenia owes its origin to an accidental observation made by Sakel in his treatment of morphine addicts. First, he noticed that the insulin hypoglycemia had a calming effect on the motor restlessness of these patients. Then, in trying out the treatment in patients with varied psychotic conditions, he observed that in schizophrenic patients the quieting effect was most pronounced. While this observation was used by Sakel as the point of departure for the insulin shock treatment, he worked out a special therapeutic procedure to be used in schizophrenic patients.[1] Subsequently, the original method has undergone considerable modifications introduced by Sakel himself and by other investigators.[2, 3, 4]

The object of this paper is to record our experience with the following aspects of insulin shock therapy:

1. Sensitivity to insulin.
2. Reactions following individual injections of insulin.
3. Unusual reactions during and following termination of individual treatments. Hazards attached to the treatment.
4. Biochemical studies.

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We are indebted to the Supreme Council, 33° Scottish Rite Masons of the Northern Jurisdiction, U. S. A., for the financial help granted for our research work on schizophrenia.

5. Electroencephalographic studies.
6. Therapeutic results.

1. *Sensitivity to Insulin.* From studies on experimental diabetes in animals and from clinical experience with diabetic patients, one knows that both men and animals may be hypo- or hyper-sensitive to insulin. Schizophrenic patients, like normal individuals and diabetics, also differ in their tolerance to insulin. Thus, in our experience the amounts of insulin which were necessary to provoke the so-called shock or hypoglycemic reactions varied from 25 to 400 units. Doses of 25 and 35 units consistently provoked profuse perspiration, very marked salivation and deep coma in three patients, 31, 60, and 46 years old; the duration of their illnesses was respectively, 6 months, 14 and 13 years. In contrast to the low tolerance for insulin in these three patients, a high tolerance was observed in two others, 16 and 17 years old, in whom the duration of their illnesses was respectively 17 and 18 months. In the 16-year-old patient not less than 200 units was necessary to provoke coma. In the 17-year-old patient, the dose which for a certain period consistently caused coma was 195 units. Then, smaller amounts, down to 100 units, had the same effect. This patient illustrates the fact that the tolerance to insulin may change considerably throughout the treatment.

2. *Reactions Following Individual Injections of Insulin.* The functions of both vegetative and somatic organs are more or less markedly disturbed following the administration of amounts of insulin high enough, according to the individual tolerance, to provoke untoward effects.

The most common reactions, under the control of the vegetative nervous system, are profuse perspiration and abundant salivation, the two reactions usually going on simultaneously. Some patients, however, while perspiring mildly or even remaining consistently dry, salivate considerably nevertheless and otherwise react intensively to insulin.

The cardiovascular system responds with marked fluctuations in the pulse rate. Bradycardia, with diminution of 20 to 30 beats, is usually first to occur; it is followed by return of the pulse rate to its original level, or by tachycardia—increases of 40 to 60 beats—in case the patient becomes restless. During coma, the pulse rate again fluctuates between levels below and above the starting point. Weakness and irregularity of the pulse are quite marked at times. Intermittent flushing of the face is of very frequent occurrence. Cyanosis of the face is observed in some patients inconsistently throughout the treatments. The blood pressure usually remains within physiological variations.

The respiratory system usually does not show significant changes in the precomatose phase of the treatment; the maximum fluctuation in the respiratory rate in one of our patients was from 18 to 28. In the comatose state, however, irregular, stertorous and deep heavy breathing are of frequent occurrence.

The body temperature more often than not goes down, and in some of our patients quite markedly. Thus, in one patient the rectal temperature dropped before the comatose phase in the course of several treatments from around 99° to 97.8° and 94°. Similarly, in another patient, the change of the temperature was from 98.3° to 93.2° in one treatment, and from 97.4° to 91.6° in another treatment. In contrast to these findings, an elevation of the axillary temperature from 97° to 102.6° was observed five hours after the termination of treatment, in a patient who was extremely restless and had generalized convulsions during the treatment. The physical examination was negative. The next morning the temperature was 98.4°.

The pupils remain either unaffected or dilated most of the time during the treatment; marked myosis occurs rather seldom. General muscular relaxation or rigidity is to be found frequently before the onset and during the comatose state. One patient, 28 years old, after the termination of a treatment with intravenous glucose could not grasp or hold objects with his right hand. This condition gradually cleared up within three hours. Tremor of the hands, and muscular twitchings particularly around the mouth, occasionally occur during the comatose state. In the precomatose phase, chills are of more frequent occurrence.

Abolition of the corneal reflexes, weakening of the plantar reflexes or a more or less marked extension of the big toe are quite common reactions during coma.

The most dramatic reactions and the ones which occur very frequently are excitement, motor restlessness, localized or more or less generalized clonic convulsions, and drowsiness, irrespective of whether or not the patient eventually goes into coma. In some patients muscular twitchings or frank convulsions originate either on the right side of the face or in the upper limbs or in both legs; they remain localized there, or culminate in generalized convulsions. Out of our 140 treated patients, 46 had convulsions during one or more individual treatments. While the proponents of the insulin treatment have changed their viewpoint in that they no longer regard convulsions as undesirable reactions, we found it beneficial, on certain occasions, to decrease their frequency or to reduce them to rather mild muscular twitchings with the help of sodium luminal; the hypnotic also offered the advantage of advancing the beginning of coma.

The reactions so far described usually occur in the following sequence: Perspiration and bradycardia become more or less pronounced within the first or second hour after the insulin injection. This is, usually, the phase of complete or relative calm; the quietness, however, is not infrequently disturbed by restlessness varying in intensity and duration and occurring also in patients who do not have convulsions. During the ultimate phase of, supposedly, supreme quietness (coma) localized or generalized convulsions may take place.

Each patient usually reacts to insulin along the same pattern throughout the treatments. Yet, the quality, intensity, sequence and duration of the

CHART I

Date	September												October									
	9	10	11	12	14	15	16	18	21	23	25	30	4	9	12	14	16	21	23	26	28	30
Insulin—Units a.m.	30	30	35	40	40	50	60	60	70	70	80	80	80	80	80	80	80	80	80	80	80	80
(Pulse before insulin)								78		76		78		80		80		80			80	
Pulse								80		76		88		100		60		68			98	
								58		48		52		68		84		50			62	
Pulse weak										×	×								×			
Pulse thready											×											
(Resp. before insulin)								18														
Resp.								20														
								16														
Resp. difficult																			×			
Perspiration	/	×			/	×	×		×	×	×		×	×	×	/	/	/		×	×	×
Salivation									/													
Quiet					/			/				×					/	/				
Motor restlessness							×		/		×	/	×	×	×	×	×	/		×	×	×
Combative							×				×			×	×							
Feels pain in abdomen		/																				
Severe headache and pain in back of neck and spine																	×					
Dizziness				/									×									
Talking								/														
Moaning											×											
Comatose						/			×	×	×	×				×	×		×		×	×
Blood sugar	62	53	47	47	43	37	37	43	33	51	36						49	49	46	37	33	35
Shock terminated																						
i.v. glucose c.c.									20	15	20					20	20		20		20	30
Sugar water										×		×		×	×			×	×	×	×	×
Unable to hold objects with right hand											×								×			
Vomiting																	×					
Complains of headache																	×					
Appetite	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Pleasant and coöperative	/	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Sleep-night	×	×	/	×	×	×	×	×	×	×	×	×	×	×	×	/	×	×	×	×	×	×

reactions, all other conditions being equal, may vary not only in different patients but also in the same patient on different days. An illustration of the reactions as observed in the daily treatments during the whole period of the insulin therapy is presented in chart 1.

3. *Unusual Reactions During and Following Termination of Individual Treatments. Hazards Attached to the Treatment.* Eight out of 140 patients treated showed reactions deserving particular mention:

A female schizophrenic patient, 38 years old, received 110 units of insulin and was left in coma for one hour. She came out of coma, as usual, after the administration of glucose by nasal tube. Soon after lunch she had a generalized convulsion, followed by a cardiovascular collapse which rapidly yielded to adrenalin and intravenous glucose. Before glucose was given, the blood sugar was 122 mg. per 100 c.c. of blood. Within the next four hours, the patient had convulsions at intervals of about 20 minutes; in all there were 11 convulsive attacks. The last convulsion at 5 p.m. was followed by deep sleep, from which she awoke only the next morning, feeling well.

A female schizophrenic patient, 34 years old, was brought out of coma, as usual, with glucose given by tube. Fifteen minutes later her pulse became very weak, but it rapidly improved after the administration of adrenalin. Yet, the patient fell into coma (at about 1 p.m.) from which she came out only the next morning at 9 a.m. Within the first six hours of coma, the pulse was of good quality but rapid (120 to 140); the body temperature reached 103.2°; the blood sugar determined three times was 33, 47 and 53 mg. per 100 c.c. of blood in spite of many administrations of glucose by tube and vein. A spinal puncture done about five hours after the onset of coma had a calming effect on the patient's restlessness; the spinal fluid sugar was 143 mg. per 100 c.c. of blood. The patient's reaction to the treatments is also worth noting—when out of coma, she usually asked how many times she would have to die and added that she was happy at being again alive.

A female schizophrenic patient, 26 years old, on one occasion while her treatment was being terminated with intravenous glucose, stopped breathing. The apnea lasted three minutes yielding to artificial respiration and caffein.

Three schizophrenic patients (one female and two males) throughout their treatment were usually brought out of coma by glucose given by tube after they remained in coma for 1 to 1½ hours. In each of them, in one treatment, the coma was unintentionally prolonged from 8 to 10 hours.

A white male patient reacted with coma to 115 units of insulin. No unusual reactions were noticed before and during the comatose state. In four successive treatments he was easily brought out from coma with the usual gavage of sugar. The next treatment with the same dose of insulin was marked by very unusual and very dramatic reactions. After the patient remained in coma for 1 hour and 15 minutes his pulse rate suddenly dropped from 130 to 76. He was immediately given glucose by nasal tube. Ten minutes later he showed slight cyanosis and a rather weak pulse. The cyanosis rapidly increased; the pulse became weaker and rapid; the respiration grew more and more labored and its rate rose to 60 per minute. Then the body temperature went up to 106° (F.) by rectum. Intravenous glucose, adrenalin, caffein, coramine, and therapeutic doses of metrazol had no apparent effect. During the 48 hours following the onset of coma, it was necessary to give the patient considerable amounts of oxygen. After 24 hours of deep coma, the patient showed signs of improvement; the temperature dropped to 101.4°, and the respiratory rate went down from 60 to 36. Pulse and blood pressure showed no significant changes. The patient remained in a

semi-comatose state for nine more days. The body temperature gradually decreased and reached a normal level two weeks after the onset of coma.

The unexplained very prolonged coma and the other very serious complications had no therapeutic effect.

A 23-year-old male schizophrenic patient underwent a thorough physical examination—according to our usual procedure—before insulin therapy was instituted. No unusual findings were elicited.

From October 4 to October 25, 1938, the patient had 15 treatments. He reacted with coma in seven treatments with 65 to 90 units. During one treatment with 75 units he had a severe convulsion lasting 46 seconds. On October 25, the sixteenth day of the treatment, the patient was given 90 units at 7 a.m. At 9:20 a.m. myoclonic movements were noticed; they subsided by 9:30 a.m. At 9:45 a.m. the patient's pulse suddenly rose to 150 and a severe convulsion lasting 26 seconds followed. He was immediately given glucose by vein and nasal tube. At 10:08 he suddenly stopped breathing. Artificial respiration was instituted and adrenalin, caffein, coramine and intravenous glucose were given. By 11:50 a.m. he was responding to questions and was groaning: "Oh, my God." At 1 p.m. he suddenly became more cyanotic. Artificial respiration and stimulants had no effect and by 1:25 he was pronounced dead. The post mortem by Dr. Langenstrass of St. Elizabeths Hospital revealed the following outstanding findings:

Gross: Acute dilatation of the heart. Extreme flaccidity of the myocardium and some turbidity.

Microscopic: Myocardium, liver, kidneys—intense, patchy congestion, areas of capillary stasis, swelling of parenchymal cells. Brain—moderate congestion, widely scattered, minute blood extravasations; one small leptomeningeal hemorrhage over cerebellum.

4. *Biochemical Studies.* In a previous study [5] 32 variables were analyzed in blood before the administration of insulin and during coma (table 1). Those variables marked with asterisks showed changes beyond normal

TABLE I

Blood Constituents Studied in Insulin Therapy

1 Total protein	*11 Fermentable sugar	22 Cholesterol
2 Albumin	12 Sodium	23 Vitamin C (ascorbic acid)
3 Globulin	*13 Potassium	24 Hemoglobin
4 Non-protein nitrogen	14 Calcium	25 RBC count
*5 Urea nitrogen	15 Magnesium	26 Vol. pkd. RBC
6 Uric acid	*16 Serum solids	27 Mean corp. vol.
7 Creatinine	*17 Phosphorus (inorg.)	*28 WBC count
8 Total creatinine	18 Chlorides	*29 Differential count
*9 Amino acid nitrogen	19 CO_2 comb. power	30 Sedimentation test
*10 Sugar	20 CO_2 content	*31 Viscosity
	*21 Lactic acid	32 Clotting time

* Constituents which showed changes during the insulin coma.

fluctuation and errors of the methods. Moreover, serum solids, potassium, phosphorus and sugar were analyzed in specimens of blood obtained at certain intervals following the administration of insulin (charts 2 and 3).

The main object of the present biochemical study is to supplement and at the same time test the accuracy of our previous findings by data obtained in another group of patients. Inasmuch as the results derived from this study

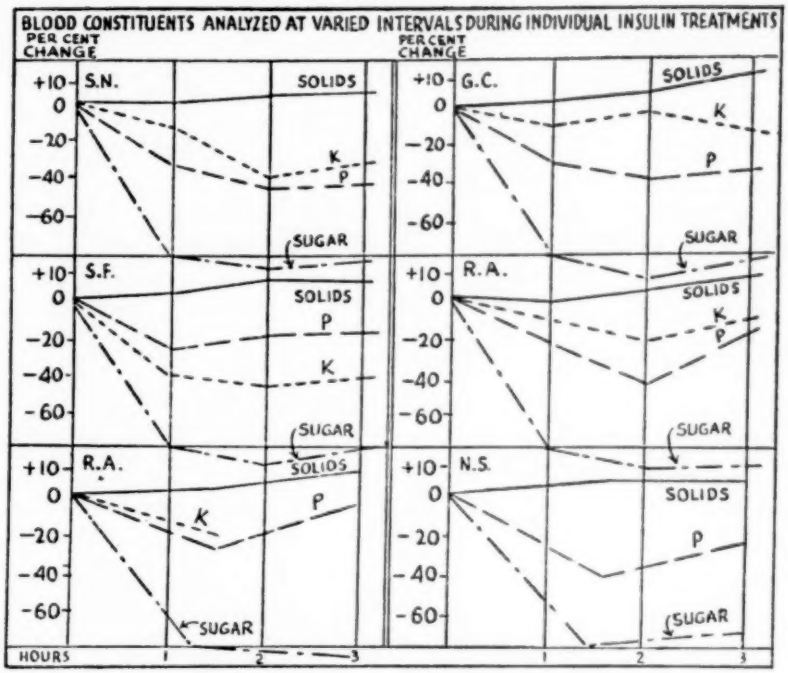

CHART II

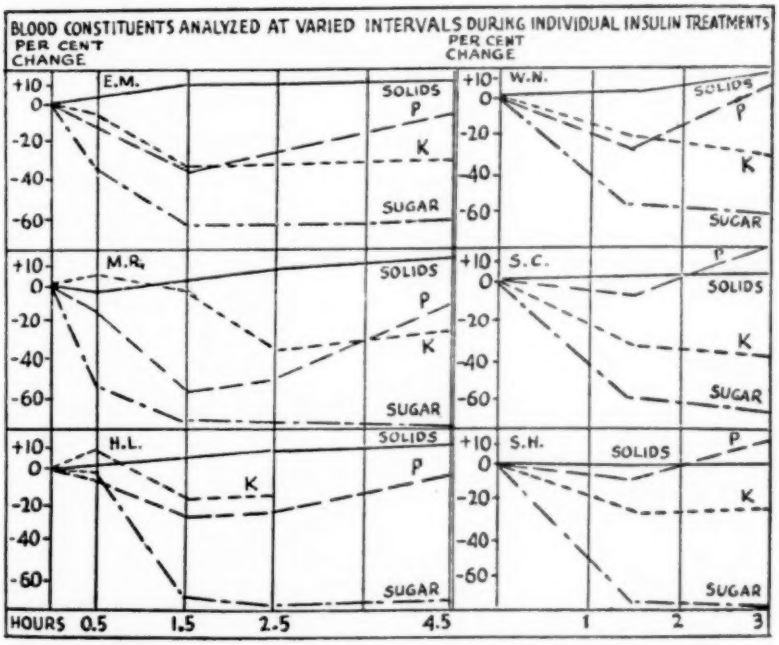

CHART III

TABLE II

Blood Constituents Which Showed Changes During the Insulin Coma

	Cases No.	Tests No.	Decrease			Increase		
			Over 25%	10% to 25%	0% to 10%	0% to 10%	10% to 25%	Over 25%
Reduc. subst.	23	23	23 (25 to 90%)					
Ferment. sugar	16	16	16 (35.9 to 94%)					
Phosph. (inorg.)	39	46	14 (25 to 45%)	12	10	3	7	
Potassium	26	27	5 (25 to 45%)	13	8	1		
Amino acid N.	21	21	4 (26.9 to 34.4%)	11	3	2	1	
Urea nitrogen	9	9		5	4			
Viscosity	11	11			3	2	6	
Serum solids	20	22			1	15	6	
Lactic acid	8	12	1 (35%)			2	1	8 (25 to 239%)
WBC count	13	14						14 (50 to 368%)
Segm. neutro.	13	14				3	3	8 (25 to 77%)
Lymphocytes	13	14	12 (25 to 83%)	2				

proved to be similar to those of a former study,[5] we combined them in table 2. In addition we again examined serum solids, sugar (total reducing substances), fermentable sugar, inorganic phosphorus and amino-acid nitrogen in blood, before and at intervals of 1, 2, and 3 hours after the administration of insulin; the last or the last two specimens of blood were obtained during the comatose state. The study was done in 11 patients and 5 controls. The results obtained in each case are presented in three charts (4, 5 and 6).

Comment. A glance at the charts shows that the curves in the control studies are markedly different from the insulin curves. The serum solids were determined chiefly for the reason that in case of an apparent increase in the concentration of blood constituents the profuse perspiration very common in this treatment would raise the question whether the increase is wholly or partly due to increased specific gravity of blood. Notwithstanding the distinct tendency of the serum solids to increase, the other blood constituents show essentially a more or less marked but very definite decrease. The decrease is followed by a trend towards the original level; in some cases phosphorus rises above the starting level.

Sugar and fermentable sugar, as one would expect, considerably diminish and remain at a low level throughout the individual treatments. The simultaneous reduction in the blood content of sugar and inorganic phosphorus is of interest, since it was suggested that the insulin hypoglycemia might be due to the formation of some substance related to hexose phosphate. The curves of sugar and phosphorus do not keep pace, however, throughout, the former remaining low and the latter gradually rising to the original level and in some cases above that level.

The relationship between the hypoglycemia, the patient's reactions, and the dose of insulin is also worth noting: The kind and severity of the pa-

tient's reactions, the degree of the hypoglycemia and the dose of insulin are not consistent in their relationships—either qualitative or quantitative ones—in different patients and in the same patient in different individual treatments.

5. *Electroencephalographic Studies.* Brain action potentials were studied in 17 schizophrenic patients under the insulin treatment.

The apparatus used consisted of a single channel push-pull condenser-coupled amplifier and ink writing oscillograph constructed in our own laboratory (by Dr. Robert Cohn), according to the design introduced by Davis

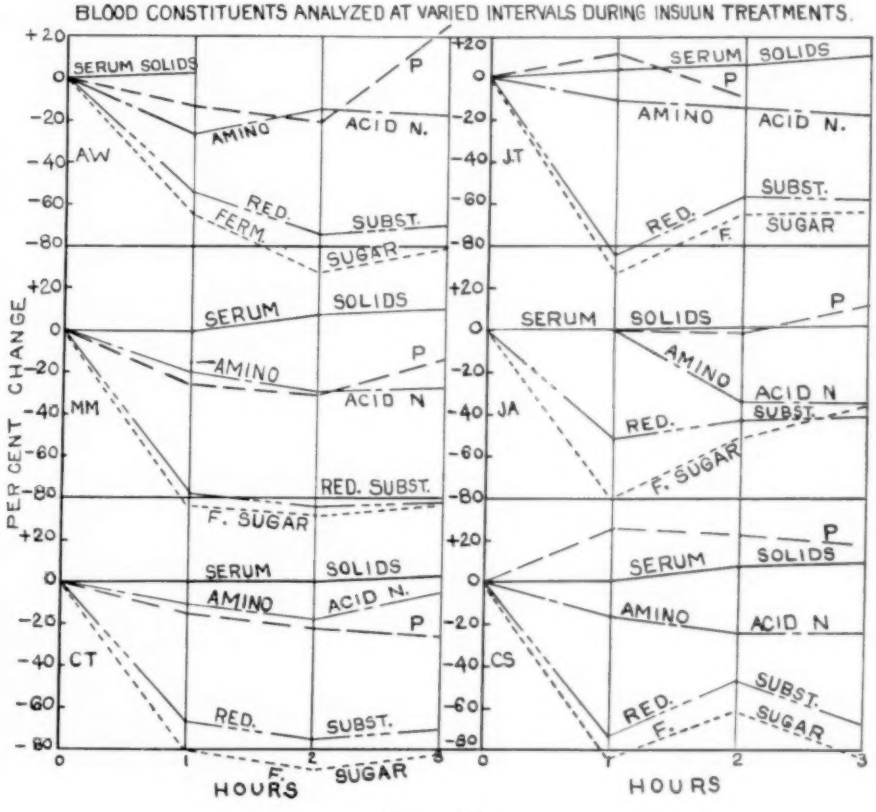

CHART IV

and Grass. The linear frequency response of this apparatus, within 1 mm., is from 2.5 to 25 cycles per second. The discharge time (time constant) is 0.2 second. Electrodes were uniformly placed over the midfrontal and midoccipital regions of the head.

From a total of 50 records, two quite distinct types of "brain waves" were noted:

The one type observed in 42 records is seen in chart 7. The time, in minutes, noted under each strip of record indicates the time elapsed from

the first strip to each succeeding strip. In the two figures presented, the first strip in each figure corresponds to the earlier period of recording which was within two hours of the insulin injection. Chart 7 may be described as follows: A fairly normal alpha rhythm, 8–10 cycles per second predominated during the earlier interval of recording. This was followed by a gradual but steady decrease in the frequency of the brain waves as the hypoglycemia progressed. Within a few hours from the time of insulin injection a low frequency brain wave pattern averaging 3-cycles per second became frankly

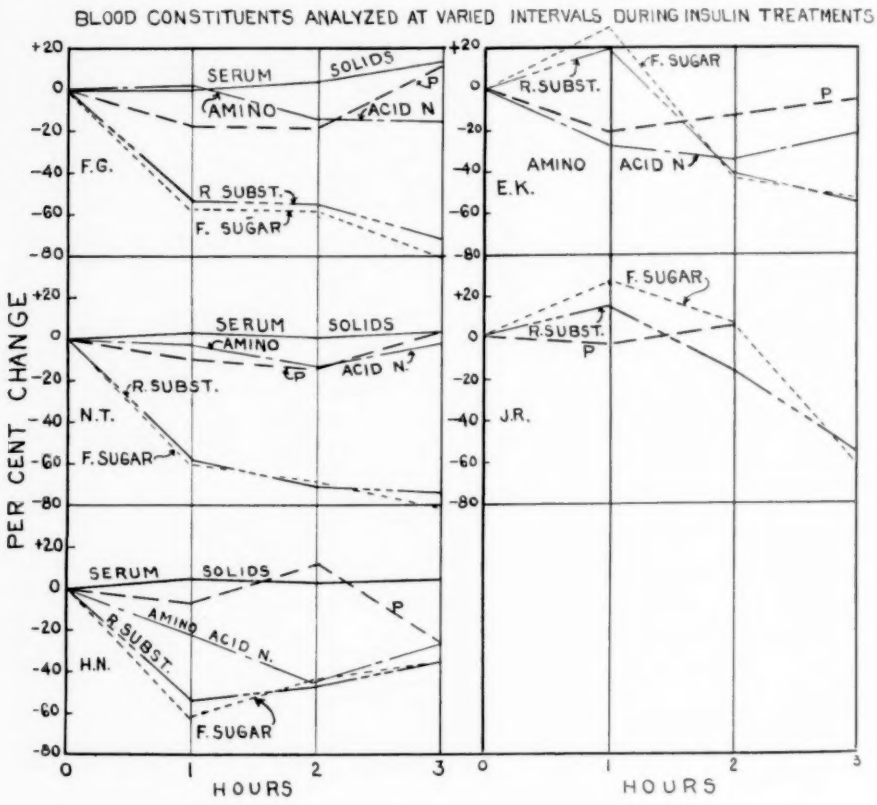

CHART V

predominant. It is interesting to note that these slow, relatively high voltage waves seemed to be independent of whether the eyelids were open or closed. Even a light flashed on the eyes gave rise to no distinct change in the brain wave pattern.

The other type of brain wave pattern (chart 8) was observed in 8 records. First, the frequency of the alpha wave pattern was around 10 cycles per second; this was followed by a 4 to 5 cycle per second rhythm. Then again, this slow wave pattern changed to a rhythm of about 10 cycles

per second. These fluctuations took place quite irregularly, usually 2 to 5 times during the entire recording.

In both types of brain wave patterns during most of the slow wave stage the patient appeared to be in deep coma. The eye reflexes were usually absent; the breathing was deep, regular and noisy; no response to auditory or tactile stimuli could be elicited. During some of the alpha wave stage of

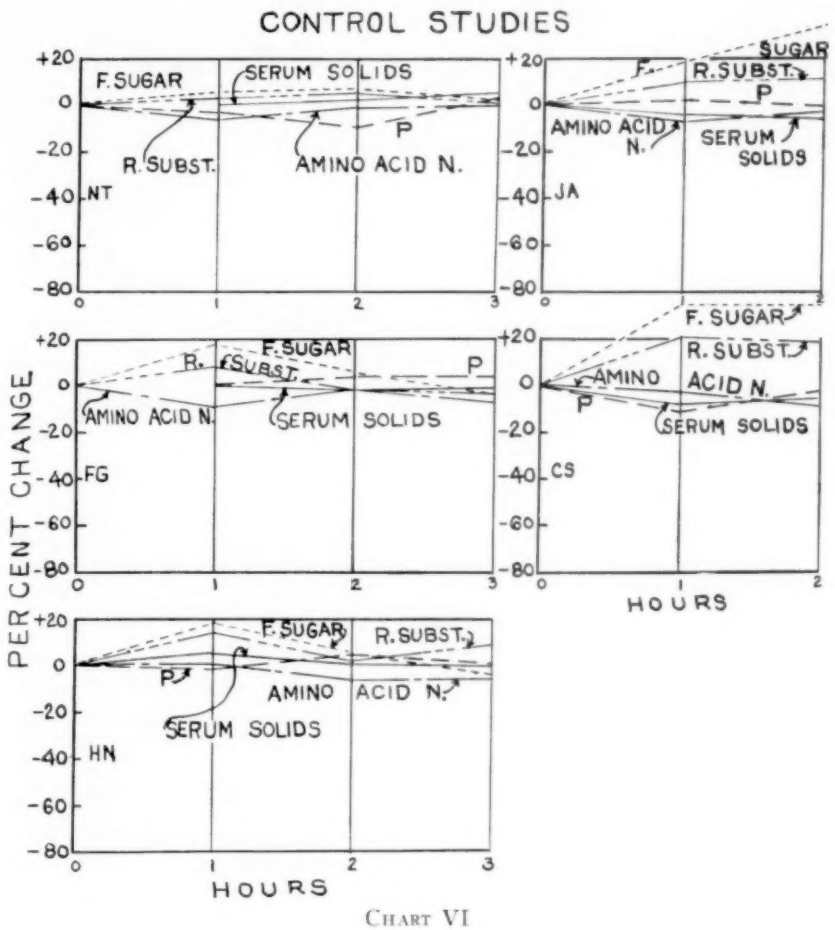

CHART VI

the second type of brain wave pattern these individuals seemed alert, and in at least two instances the subject was more lucid and accessible than usual.

There was a striking parallelism between the variations in the brain potentials and the changes in the blood sugar content. Thus, with intravenous glucose the return of the brain wave pattern to the original preinsulin type was quite rapid—often within ten minutes; with gavage the return to the original pattern was usually longer, but not exceeding 30 minutes after the administration of glucose.

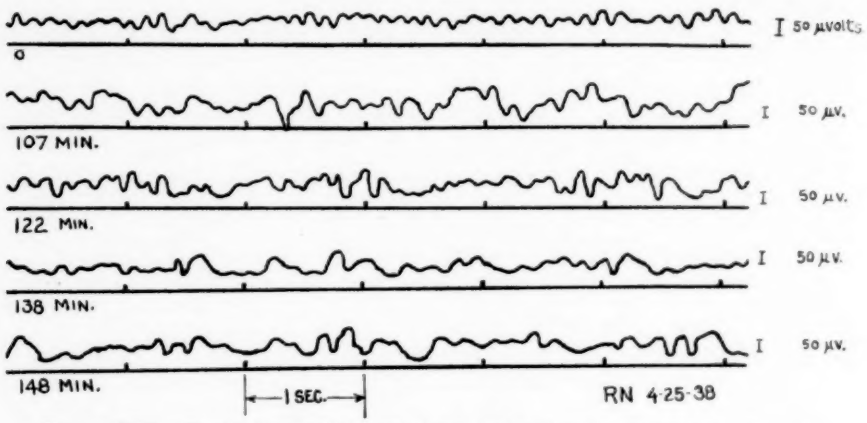

CHART VII. Cortical potential variations during insulin treatment. Type I

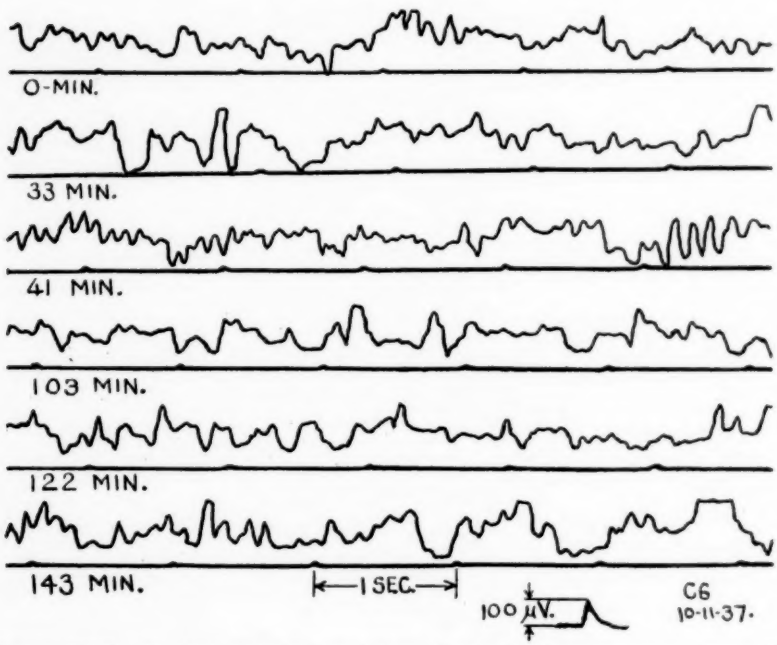

CHART VIII. Cortical potential variations during insulin treatment. Type II

6. *Therapeutic Results.* In evaluating the therapeutic results obtained in our schizophrenic patients we considered only one aspect, namely the duration of the illness. *Remission* signifies complete freedom from psychotic symptoms and satisfactory adjustment outside of the hospital. *Improvement* implies markedly favorable change in the patient's behavior, satisfactory social adjustment in the hospital and under certain favorable circumstances even outside of the hospital. The tabulated results are self-explanatory (table 3).

TABLE III

Therapeutic Results Obtained with Insulin Treatment in 140 Schizophrenic Patients

Duration of Illness	No. of Cases	Remission	Improvement	No Change
Under 6 mos.	28	16* (one for 6 weeks) (one for 1 mo.)	3	9
6 to 12 mo.	36	8 (one for 3 mos.)	9	19
1 to 2 years	26 (1 death)	5	6	14
2 to 3 years	13	3	3	7
3 to 6 years	27	3	3	21
6 to 10 years	3			3
10 to 19 years	7		1	6
Total	140	35	25	79

* In one case the remission occurred 1 mo. after treatment was discontinued.

CONCLUSIONS

This treatment has already given room to such a formidable number of publications that a synthesis is indicated not on the basis of studies of any one group of investigations but on the basis of comparative critical studies of material obtained by a great many investigators and from varied sources.

Therefore, we prefer to abstain from conclusions in the light of our own data, hoping that these data might be used with benefit for further comprehensive studies and reviews of the literature.

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THE ANTICATALASE ACTIVITY OF SULFANILAMIDE AND SULFAPYRIDINE IN VIVO *

By MARTIN CLYMAN, M.D., *Philadelphia, Pennsylvania*

AN anticatalase activity of sulfanilamide in concentrations in vitro equivalent to those found in vivo during sulfanilamide therapy, was first observed by Main, Shinn and Mellon.[13] In extending these observations Locke, Main and Mellon [11] have concluded that hydrogen peroxide, which accumulates due to the diminished catalase activity, and not the sulfanilamide per se, is the active agent in combating bacterial infections. Hydrogen peroxide in pneumococcus cultures (Type 1, 18 hr. growth) was estimated by Shinn, Main and Mellon [25] who were able to detect concentrations as small as 0.0003 per cent. Retardation of growth of cultures containing sulfanilamide was accompanied by an increase in hydrogen peroxide as compared with the controls.[14]

Catalase is inactivated by hydroxylamine and chemically related compounds.[2, 9] Locke, Main and Mellon [11] claim that analogous anticatalase substances are produced from sulfanilamide when dilute solutions of the drug are exposed to ultraviolet irradiation. The anticatalase activity of the irradiated drug shows a marked increase with the development of the violet color which was first described by Ottenberg and Fox.[13, 23] This colored derivative of sulfanilamide (an oxidation product) forms a redox system which is present in the blood after sulfanilamide therapy (Fox, German and Janeway [5]). Mayer [18] found the para-hydroxylamine of benzenesulphonamide to be many times more active than sulfanilamide in vitro and in vivo. He believes this oxidized derivative of sulfanilamide to be the active agent formed in vivo.

Sulfanilamide produces unfavorable oxidation reduction potentials for the growth of hemolytic streptococci.[5, 27] Catalase lowers the electrode potential of a culture by decomposing hydrogen peroxide.[7] The facultative anaerobes, the streptococci and pneumococci are among the chief catalase producers and also are among the most active formers of peroxides.[19, 20] The addition of catalase to a culture of *Streptococcus hemolyticus* containing sulfanilamide reduces the bacteriostatic effectiveness of the drug. This is brought about by lowering the electrode potential, whereas sulfanilamide bacteriostasis is accompanied by an elevation in electrode potential, and normal growth by a rapidly falling potential.[5] The addition of 0.02 per cent hydrogen peroxide (in physiologic saline) to a culture of *Streptococcus hemolyticus* produces a lag phase in the growth of this organism in vitro, by

* Received for publication March 18, 1940.
Awarded the Chas. W. Burr prize for internes of the Philadelphia General Hospital, June 1939.

elevating the electrode potential.[5, 6, 8] Sulfapyridine affects the electrode potential in the same manner.[27]

The enzyme catalase has recently been isolated in crystalline form by Sumner and Dounce [26] and is shown to be an iron porphyrin compound. Bacteria devoid of iron porphyrin compounds live by an anaerobic fermentation process. The streptococci and pneumococci are facultative anaerobes, and sulfanilamide does not act on these organisms if air is excluded from the cultures.[5, 27] Thus under anaerobic conditions these organisms continue to grow in the presence of sulfanilamide. This phenomenon may be explained in three ways: (1) peroxide is formed in aerated cultures of hemolytic streptococci, and not under anaerobic conditions [6]; (2) in complete absence of molecular oxygen the activity of catalase is completely abolished [10]; (3) the electrode potential is lowered in sterile broth in the absence of oxygen [3, 4] and is further lowered in the presence of hemolytic streptococci.[6] This absent activity of sulfanilamide under anaerobic conditions occurs in vivo as well as in vitro.[12] McLeod and Gordon [19] found that anaerobes that do not produce catalase are particularly susceptible to hydrogen peroxide.

With the available evidence of the influence of catalase on bacterial growth and the anticatalase effect of sulfanilamide in vitro, it appeared desirable to investigate quantitative changes in catalase in patients and animals receiving sulfanilamide or sulfapyridine.

Methods

Blood catalase determinations were done on 21 patients. Fifteen subjects were receiving sulfanilamide or sulfapyridine, one patient was receiving antipneumococcal serum, and five received neither sulfanilamide, sulfapyridine nor serum. Since in studying the in vitro anticatalase effect of sulfanilamide Shinn, Main and Mellon [25] had employed cultures of pneumococci, nine proved cases of lobar pneumonia (pneumococcus) were included among the 15 cases selected for treatment. Samples of oxalated blood obtained by venipuncture were examined quantitatively for catalase before, during and after the administration of sulfanilamide or sulfapyridine, the blood levels of the drugs used being determined simultaneously. Striking changes were observed. The results obtained in man were confirmed under controlled experimental conditions in rats.

The catalase determinations were done by the method of Bach and Zubkowa,[1] modified by using Sorensen's phosphate buffer (pH 6.8) instead of distilled water in the reaction mixture. This was done because of the work of Morgulis [21] who found that in the presence of sufficient buffering, the catalase reaction becomes directly proportional to the concentration of the enzyme, and independent of the hydrogen peroxide concentration, the optimum pH being 6.8 with an active range of 6.5 to 8.5. The determinations of sulfanilamide and sulfapyridine blood levels were done by the method of Marshall and Litchfield.[16] The normal range of catalase values obtained by

Bach and Zubkowa were 14 to 18 units (where the catalase value = mg. of hydrogen peroxide decomposed by 0.001 c.c. of blood and 1 unit = 1 mg. of hydrogen peroxide.) Values obtained by the writer on normal individuals, varying in age from 1 to 80 years, ranged from 16 to 20 units. The catalase values for each normal individual remained remarkably constant.

In animal experiments, nine rats (free of *Bartonella muris*) were employed. Five were treated with sulfanilamide; the remaining four served as controls. The rat was selected instead of the mouse because the excretion of sulfanilamide is slower and the drug can be maintained at the desired levels much more easily.[17]

The treated rats were given 0.4 gm. of sulfanilamide per kilo. per 24 hours in two doses of 0.2 gm. per kilo., at 9:30 a.m. and at 1:30 p.m. by subcutaneous route, using a 1 per cent solution of sulfanilamide (37.5° C.) in physiologic saline solution (sterile). The four controls received the same amount of saline in the same manner and at the same time. This was repeated for four successive days. Blood was taken from the tail at 5:00 p.m. Sodium oxalate was used as the anticoagulant; 0.02 c.c. was used for catalase determinations and 0.1 c.c. was used for sulfanilamide determinations where all reagents for the determination were proportionately reduced to 1/10. Centrifugation was used in place of filtration. All determinations were done in duplicate.

Results

All of the 15 patients except one showed a definite depression of the blood catalase activity. In contrast, the five controls showed practically no diminution of blood catalase activity. Eight of the treated patients showed a decrease of catalase activity of 20 per cent or more. The decrease occurred as soon as 12 to 24 hours after the administration of either sulfanilamide or sulfapyridine, reaching its lowest levels in 24 to 72 hours. Low levels of blood catalase values were obtained during the administration of the drug, the catalase activity usually returning to pretreatment levels after the drug was withheld, but in a more gradual manner. Although suggestive, no direct relationship could be established in these treated patients between the occurrence of minimum catalase values or persistence of low catalase values and the blood sulfanilamide or sulfapyridine levels. This can be seen by referring to table 1. Patient 1 shows a 47 per cent decrease in catalase activity with an 8 mg. per cent sulfapyridine blood level, and patient 12 a decrease of 44 per cent, with a blood level of sulfanilamide of 1 to 3 mg. per cent. This is in contrast to patient 7 who shows a 17 per cent decrease in catalase activity with a sulfapyridine blood level of 16 mg. per cent. Shinn, Main and Mellon [25] found, in studies of anticatalase activity of sulfanilamide made in vitro, a maximum suppression of catalase activity in 2 mg. per cent solutions of sulfanilamide. One patient, number 10, responded to sulfanilamide with a rise in blood catalase activity. This was a mild case

of pharyngitis in a four year old negro, who was not acutely ill, but who responded well to treatment clinically with sulfanilamide. A maximum blood level of 4 mg. per cent was obtained.

No definite correlation could be established between the maximum percentage suppression of blood catalase activity, the dose of the drug given and the number of days treatment. Again referring to case 1, 22.5 gm. sulfapyridine given over a period of six days resulted in a 47 per cent diminution of blood catalase activity; and in case 8, 15 gm. given over four days resulted in a 40 per cent diminution of blood catalase activity.

TABLE I

Patients Receiving Sulfanilamide, Sulfapyridine, or Serum

Case No.	Age Yrs.	Sex	Diagnosis	Date (1939)	Treatment	Total Amount of Drug Grams	Blood Level of Drug Mg. %	Catalase Units
1	10	M.	Lobar pneumonia	Feb. 1	Before		0	18.2
				Feb. 1	Sulfapyridine	22.5	7	14.7
				Feb. 3	Sulfapyridine		8	12.9
				Feb. 6	Sulfapyridine		9	16.8
				Feb. 11	After		3	9.6
				Feb. 11	After		Trace	19.1
2	15	F.	Lobar pneumonia	Feb. 6	Before		0	12.9
				Feb. 8	Sulfapyridine	12.5	8	11.0
				Feb. 10	Sulfapyridine		12	15.2
				Feb. 13	After		Trace	11.0
				Feb. 15	After		0	14.0
3	27	M.	Lobar pneumonia	Feb. 6	Before		0	18.2
				Feb. 9	Sulfapyridine	32	8	14.0
				Feb. 11	Sulfapyridine		12	14.7
				Feb. 13	After		1.4	14.1
				Feb. 15	After		Trace	18.2
4	2	M.	Bilateral otitis media	Feb. 10	Before		0	17.2
				Feb. 13	Sulfanilamide	16	3	13.4
				Feb. 15	Sulfanilamide		1.3	14.7
				Feb. 18	Sulfanilamide		1.8	16.8
				Feb. 19	After		Trace	17.2
				Feb. 21	After		0	18.2
5	1.5	M.	Acute pharyngitis	Feb. 9	Before		0	17.2
				Feb. 10	Sulfanilamide	10	7	15.2
				Feb. 13	Sulfanilamide		9	12.4
				Feb. 15	After		1.8	15.4
				Feb. 16	After		Trace	16.8
6	3	M.	Lobar pneumonia	Feb. 9	Before		0	15.9
				Feb. 11	Sulfapyridine	11	6	14.3
				Feb. 13	Sulfapyridine		8	12.7
				Feb. 15	After		1.4	12.9
				Feb. 18	After		Trace	14.4
				Feb. 20	After		0	16.1
				Feb. 22	After		0	16.4
7	55	M.	Lobar pneumonia	Feb. 9	Before		0	15.9
				Feb. 11	Sulfapyridine	20	16	13.3
				Feb. 13	Sulfapyridine		14	16.2
				Feb. 15	After		4	15.0
				Feb. 16	After		1	16.2
8	9	M.	Rheumatic fever	Feb. 11	Before		0	18.2
				Feb. 13	Sulfapyridine	15	12	11.0
				Feb. 15	Sulfapyridine		19	13.6
				Feb. 18	After		2	16.1
				Feb. 20	After		0	17.3

TABLE I—*Continued*

Case No.	Age Yrs.	Sex	Diagnosis	Date (1939)	Treatment	Total Amount of Drug Grams	Blood Level of Drug Mg. %	Catalase Units
9	44	M.	Lobar pneumonia	Feb. 10	Before		0	16.5
				Feb. 11	Sulfapyridine	20	12	13.7
				Feb. 13	Sulfapyridine		15.5	12.7
				Feb. 15	After		2	18.2
10	4	M.	*Streptococcus hemolyticus* pharyngitis	Feb. 11	Before		0	16.5
				Feb. 12	Sulfanilamide	7	4	16.5
				Feb. 13	Sulfanilamide		3.5	17.2
				Feb. 15	After		2	18.5
				Feb. 18	After		0	19.2
				Feb. 21	After		0	20.6
11	58	M.	Lobar pneumonia	Feb. 13	Before		0	18.9
				Feb. 15	Sulfapyridine	24	9.8	16.1
				Feb. 16	Sulfapyridine		8	16.4
				Feb. 18	After		7	18.2
				Feb. 20	After		2	18.2
12	6	M.	Otitis media	Feb. 16	Before		0	23.1
				Feb. 17	Sulfanilamide	10	3	13.6
				Feb. 18	Sulfanilamide		1	12.9
				Feb. 20	Sulfanilamide		0.8	19.9
				Feb. 21	After		Trace	18.2
				Feb. 22	After		0	18.9
13	12	M.	Lobar pneumonia	Feb. 13	Before		0	18.2
				Feb. 15	Sulfapyridine	20	4.6	16.1
				Feb. 16	Sulfapyridine		5	15.0
				Feb. 19	After		0	18.2
				Feb. 21	After		0	19.9
14	46	M.	Lobar pneumonia	Feb. 16	Before		0	16.8
				Feb. 17	Sulfapyridine	25	8	16.1
				Feb. 18	Sulfapyridine		9	14.3
				Feb. 20	Sulfapyridine		3	17.5
				Feb. 21	Sulfapyridine		Trace	17.8
15	2	M.	Naso-pharyngitis	Feb. 11	Before		0	16.1
				Feb. 12	Sulfanilamide	7	6.5	16.7
				Feb. 13	Sulfanilamide		4.8	15.4
				Feb. 14	After		1.5	16.1
				Feb. 15	After		Trace	16.1
16	46	M.	Lobar pneumonia type I	Apr. 27	Before			23.4
				Apr. 27	200,000 units			23.4
				Apr. 28	Type I anti-pneumo. serum			23.4
				Apr. 29	After			20.9
				May 1	After			18.7
				May 3	After			20.4
				May 4	After			21.7
				May 5	After			22.4

The five control cases showed negligible variations in blood catalase values.

Two patients in this series died. Case 11, a patient suffering from lobar pneumonia, treated with sulfapyridine, showed only a 16 per cent maximum diminution of catalase activity with a blood level of 9.8 mg. per cent sulfapyridine. The other, case 3, received neither drug and showed a slight elevation of blood catalase activity. This patient was in the hospital for only three days.

TABLE II

Control Patients

Case No.	Age Yrs.	Sex	Diagnosis	Date (1939)	Catalase Units
1	34	F.	Lobar pneumonia	Feb. 18	16.8
				Feb. 20	16.1
				Feb. 21	16.4
				Feb. 23	17.2
				Feb. 25	17.5
				Feb. 26	17.5
2	16	M.	Lobar pneumonia	Feb. 19	18.2
				Feb. 20	18.5
				Feb. 21	17.8
				Feb. 23	18.2
				Feb. 25	17.8
3	54	F.	Lobar pneumonia	Feb. 10	14.7
				Feb. 12	15.4
				Feb. 13	15.3
4	9	F.	Broncho-pneumonia	Feb. 16	15.1
				Feb. 18	14.7
				Feb. 19	14.3
				Feb. 21	15.1
				Feb. 23	14.7
5	6	M.	Lobar pneumonia	Feb. 15	16.8
				Feb. 17	16.2
				Feb. 18	17.2
				Feb. 20	17.5
				Feb. 22	17.8

The clinical course of the patients treated with sulfanilamide or sulfapyridine usually paralleled the drop in catalase activity. The temperature, pulse and respirations fell and other symptoms subsided as the catalase activity dropped.

Case 16, a patient with Type 1 pneumococcal lobar pneumonia, received 200,000 units of antipneumococcus serum within two days. It is noteworthy that this patient showed a fall in blood catalase activity three days after the serum treatment was begun, reaching a maximum decrease of 21 per cent on the fourth day after treatment was initiated.

Observations Made on Rats. Rats receiving sulfanilamide showed an immediate drop in blood catalase values simultaneously with the administration of sulfanilamide. The maximum diminution occurred 24 hours after sulfanilamide was discontinued. Blood sulfanilamide in these rats reached a maximum of 20 to 23 mg. per cent, and the rise in blood concentration showed a definite time relationship to the low blood catalase values (figure 1). The return of blood catalase values to their previous normal levels was gradual. This sequence is similar to that observed in man.

Rats serving as controls showed only slight and variable changes in catalase values, in contrast to the marked lowering of the blood catalase value of the sulfanilamide treated rats (figure 2). The effect of sulfanilamide in its anticatalase action is more evident and uniform in the treated rats than in the treated patients. This can probably be explained by the

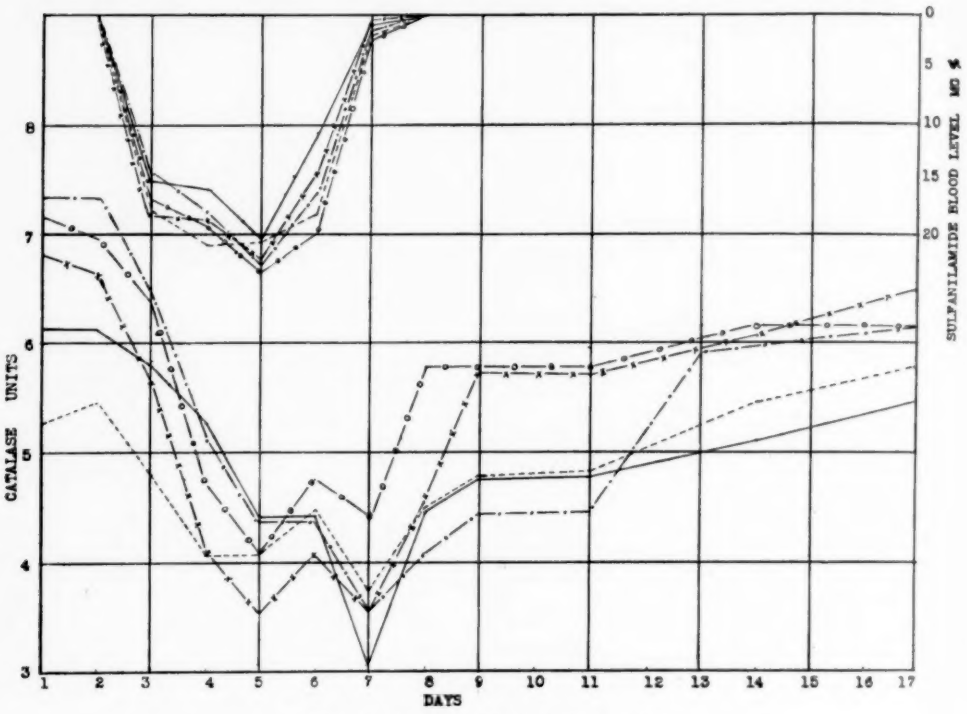

FIG. 1. Sulfanilamide treated rats.

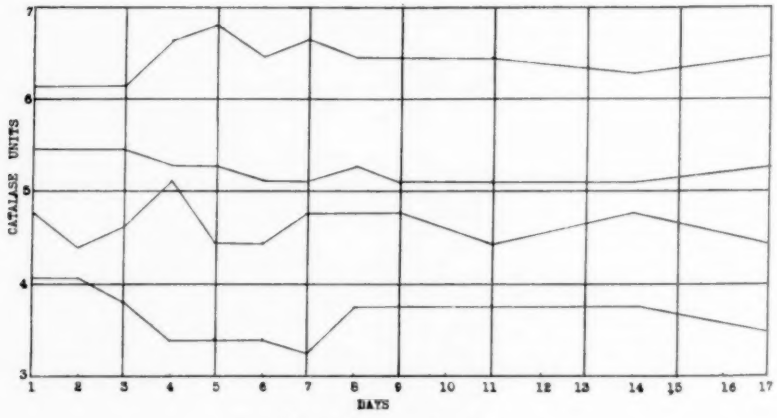

FIG. 2. Control rats.

controlled conditions of the rat experiments. The average maximum decrease of the catalase activity in the treated rats was 45.6 per cent.

COMMENT

From the above results it is evident that sulfanilamide and sulfapyridine decrease the blood catalase activity in man and rats. This demonstrates a

change in living organisms similar to in vitro observations. Although blood catalase activity is affected to a greater extent in rats, the changes in man are sufficient to permit the postulation of significant effects.

That the mode of action of sulfanilamide postulated by Locke, Main, and Mellon [11] on the basis of experiments with pneumococcus cultures can be extended to describe its action in higher animals is shown in this paper.

Thus there occurs reduction of catalase activity (and probably alterations of other enzymic systems) either by these drugs, or more likely by an oxidation product of these drugs, to levels that allow an accumulation of hydrogen peroxide in the area of infection in concentrations sufficient to raise the electrode potential of the tissues of the host. In this manner conditions are made temporarily unfavorable for normal oxidation-reduction processes of the invading organisms. The resultant bacteriostasis then enables the tissues of the host to eliminate dormant, non-metabolizing organisms by the activity of the phagocytic mechanism in the area of infection.

Summary

1. A definite diminution of the blood catalase activity in 14 of 15 patients treated with sulfanilamide or sulfapyridine has been demonstrated. A similar response has been shown to occur in rats.

2. A possible mode of action of sulfanilamide based on the anticatalase effect in vivo is described.

I wish to express my thanks to the chiefs of the Medical and Pediatric Departments for permission to study their patients, to Dr. J. H. Clark for the use of the laboratory facilities and to Drs. J. G. Reinhold and S. B. Rose for advice and criticism during the course of experimentation.

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BLOOD PRESSURE STUDIES ON UNIVERSITY STUDENTS, INCLUDING THE EFFECT OF EXERCISE ON ESSENTIAL HYPERTENSION, HYPOTENSION, AND NORMAL SUBJECTS *

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It is evident from the accumulation of articles in the scientific literature, that many factors influence the level of blood pressure. However, with our present knowledge, the cause of essential high and low blood pressures remains quite obscure.

The purpose of this investigation has been to study the normal and abnormal blood pressures among university students and to ascertain the effect of exercise upon them from a comparative standpoint. A history and physical examination are obtained on each entering student. This study included the observation of 15,500 male students at the University of Illinois from 1935 to 1939. Those with high and low blood pressure and a normal control group were rechecked at intervals. Detailed information was obtained on factors which might have an effect on the blood pressure, such as illnesses, habits, diet, family history, etc.

The students with a systolic blood pressure over 150 mm. Hg at the time of their entrance physical examination were put into the hypertension group. All students with a systolic pressure upon entrance below 108 were classified in the hypotension group. The control group consisted of matriculants with systolic pressure between 114 and 138 mm. Hg. The exercise test was not done on discernible cases of organic heart, kidney or thyroid disease.

A variation of the cold pressor test, as described by Hines and Brown [1] was done on these students. As reported elsewhere,[2] this portion of the investigation revealed: (1) The hypertensive and hypotensive classes were slower in reaching their maximum increase in the systolic and diastolic pressures; (2) there was a greater increase in the systolic and diastolic blood pressure of the hypertensive subjects than of the control group; (3) the high and low blood pressure groups returned to their basal level more slowly than did the normal subjects.

Blood Pressure Response to Exercise

The basal blood pressure and pulse were obtained by having the student rest for a 30 minute period, or until repeated blood pressure readings and the pulse rate remained at a constant basal level. All cases performed the same type of exercise, which consisted of raising the weight of the body 20 times from the floor on to a chair 18½ inches high at the rate of 40 cycles per

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minute. The student resumed his sitting position in the comfortable chair and his arm placed upon a table of convenient height. The blood pressure and pulse rate were taken at each ½ minute interval for 2 minutes, then each successive minute until the systolic and diastolic pressures and the pulse rate returned to the basal level. The 96 hypertensive, 56 hypotensive and 128 normal subjects on which the cold pressor test had been conducted for vasomotor response were used to study the comparative effect of exercise on the three groups.

The systolic blood pressure of 20 per cent of the hypertensive cases increased over 60 mm. Hg. In 2 per cent the increase was over 80 mm. Hg (table 1). The systolic pressure in the normal group failed to increase

TABLE I

Comparison of Blood Pressure Response to Exercise

Blood Pressure	Mm. Hg *increase* in *systolic* pressure *above* basal level Mm. Hg *decrease* in *diastolic* pressure *below* basal level										
	0	1–10	11–20	21–30	31–40	41–50	51–60	61–70	71–80	over	Aver.
High											
Systolic....			2.1*	18.7	10.4	27.1	20.8	12.5	6.2	2.1	48
Total†...			2.1	20.8	31.2	58.3	79.1	91.6	97.8	99.9	
Diastolic...	10.4	43.7	25.0	18.7	0	0	2.1				15
Total....	10.4	54.1	79.1	97.8			99.9				
Normal											
Systolic....			20.0	17.1	25.7	19.9	17.2				37
Total....			20.0	37.1	62.8	82.7	99.9				
Diastolic...	5.7	42.8	42.8	8.5							12
Total....	5.7	48.5	91.3	99.8							
Low											
Systolic....		8.3	25.0	58.3	8.3						23
Total....		8.3	33.3	91.6	99.9						
Diastolic...	8.3	33.3	50.0	8.3							13
Total....	8.3	41.6	91.6	99.9							

* All figures expressed in per cent of cases studied, except last vertical column which is expressed in mm. Hg, average increase in systolic and average decrease in diastolic blood pressure.

† Represents accumulative total per cent of students for each subsequent 10 mm. change in blood pressure.

more than 50 mm. in 82.7 per cent of the cases and in none did it rise more than 60 mm. In the low blood pressure group, 91.6 per cent of the subjects failed to show an increase of more than 30 mm. and in none did the pressure increase more than 40 mm. The average increase of the systolic pressure was 48, 37, and 23 mm. Hg for the hypertensive, normal and hypotensive classes, respectively. The diastolic pressure in all three groups decreased, as shown in table 1. Over 91 per cent of the cases in the normal and hypotensive classes and 79 per cent of the hypertensive subjects did not have more than a 10 to 20 mm. decrease in the diastolic pressure. Only

about 8.5 per cent of the normal and low pressure groups had a diastolic decrease of 21 to 30 mm. as compared to 18.7 per cent of the hypertensive class. Some observers have failed to find a decrease in the diastolic pressure following exercise. The decrease is very definite and it is difficult to understand just why some of the investigators were unable to discover it.

The systolic pressure following exercise returned to the basal level within 5 minutes in 100 per cent of the normal group as compared to only 78.8 per cent of the high pressure group and 74.8 per cent of low pressure groups (table 2). The diastolic pressure which fell during exercise rose to the basal level within 5 minutes in 100 per cent of the normal and hypotensive subjects as compared to only 84 per cent of the high blood pressure group (table 2).

TABLE II

Time for Blood Pressure to Return to Basal Level after Exercise

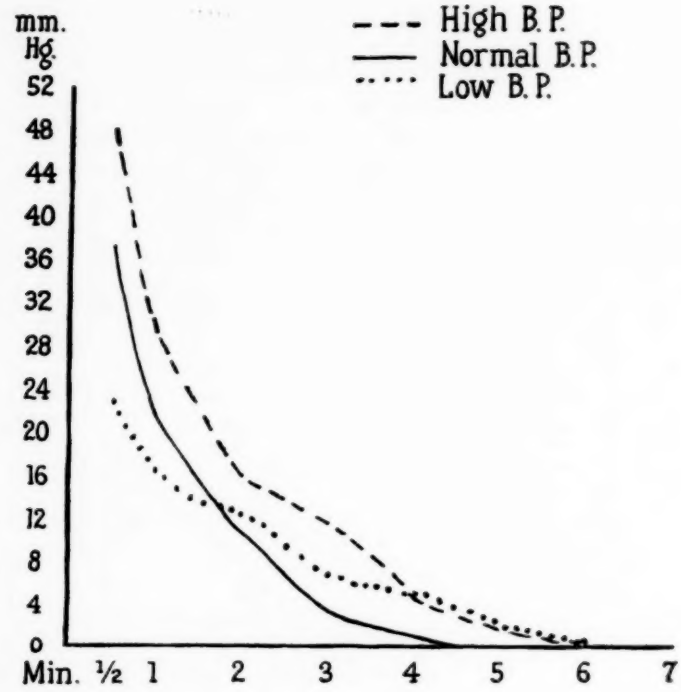
Blood Pressure	Time in Minutes								
	0	1	2	3	4	5	6	7	8
High									
Systolic			10.4*	24.2	26.3	17.9	14.7	4.2	2.1
Total†			10.4	34.6	60.9	78.8	93.5	97.7	99.8
Diastolic		2.1	14.7	27.3	25.2	14.7	11.6	4.2	
Total		2.1	16.8	44.1	69.3	84.0	95.6	99.8	
Normal									
Systolic			14.2	34.0	25.7	25.7			
Total			14.2	48.4	74.1	99.8			
Diastolic	5.8	8.8	23.5	17.6	26.5	17.6			
Total	5.8	14.6	38.1	55.7	82.2	99.8			
Low									
Systolic		8.3	8.3	16.6	25.0	16.6	8.3	16.6	
Total		8.3	16.6	33.2	58.2	74.8	83.1	99.7	
Diastolic	8.3	25.0	16.6	8.3	16.6	25.0			
Total	8.3	33.3	49.9	58.2	74.8	99.8			

* All figures expressed in per cent of cases studied.
† Represents accumulative total per cent of students for each subsequent minute.

When the blood pressure variations for the three groups are calculated for each time period (figure 1), the following information was apparent:

1. The increase in the systolic pressure following exercise was greatest in the high blood pressure group.
2. The systolic pressure in the hypertensive and hypotensive classes returned to normal more slowly than did the normal group.
3. The diastolic pressure, which decreased, returned to the basal level somewhat slower in the high blood pressure subjects (figure 2).

The pulse rate following exercise in all the normal and low pressure cases returned to the basal level within two minutes. The pulse rate also fell



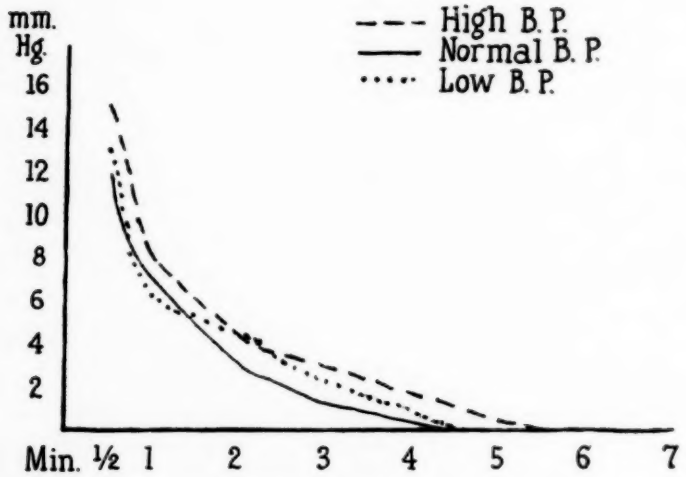


FIG. 1. Comparison of the average systolic blood pressure following exercise, showing the amount of increase and the time to return to the basal level.

FIG. 2. Comparison of the average diastolic blood pressure following exercise, showing the amount of decrease and the time to return to the basal level.

rapidly in the hypertensive class, but on the average did not reach the original rate for 3½ minutes after the exercise was discontinued. The average pulse rate increase after exercise was 30, 34, and 30 beats per minute for the high, normal and low pressure groups, respectively (table 3). The increase in the

TABLE III

The Summarized Effect of Exercise upon Blood Pressure

	High Blood Pressure		Normal Blood Pressure		Low Blood Pressure	
		P — B.P.		P — B.P.		P — B.P.
Increase in systolic pressure—mm. Hg.	48		37		23	
Decrease in diastolic pressure—mm. Hg.	15		12		13	
Increase in pulse per minute	30		34		30	
Limit cases—showing increase in pulse and systolic B.P.		6 — 60 36 — 24		54 — 18 18 — 40		22 — 28 18 — 40

blood pressure cannot be attributed to this factor alone, since many cases had a marked increase in the systolic blood pressure with only a slight increase in the pulse rate, and vice versa. For example, note the variations of the pulse and corresponding blood pressure increase of the limit cases (table 3). In one case, the pulse only increased 6 beats per minute, yet the blood pressure increased 60 mm. Hg. At the other extreme, in one of the normal subjects, the maximum pulse increase was 54 beats per minute, yet the maximum blood pressure response was only 18 mm. Hg increase. The vasomotor response from other factors appears to play a more important part in the production of the increased pressure than the increased pulse can account for.

TABLE IV

Summarization of Blood Pressure Variations from the Basal Level

Blood Pressure	Systolic Blood Pressure						Diastolic Blood Pressure					
	L. B. P.*		N. B. P.*		H. B. P.*		L. B. P.		N. B. P.		H. B. P.	
	Mm. Hg	Rise Mm. Hg	Mm. Hg	Rise Mm. Hg	Mm. Hg	Rise Mm. Hg	Mm. Hg	Ave. Change Mm. Hg	Mm. Hg	Ave. Change Mm. Hg	Mm. Hg	Ave. Change Mm. Hg
Basal B.P.	99		116		136		70		74		80	
Usual B.P.	104	5	123	7	164	28	75	5	77	3	87	7
B.P. after Exercise	122†	23	153	37	184	48	57	13	62	12	65	15
B.P. with Cold Test	110‡	11	126	10	154	18	81	11	88	14	96	16

* L. B. P. indicates low blood pressure, N. B. P. indicates normal blood pressure, H. B. P. indicates high blood pressure.

† Figures indicate average maximum blood pressure after exercise. Under each column mm. Hg.

‡ Figures indicate average maximum blood pressure with cold test. Under each column mm. Hg.

Table 4 gives a summarized average tabulation of the blood pressure observations, including the results of the cold pressor test. The diastolic pressure following exercise in each group fell about the same amount below the basal diastolic pressure level as it increased above this level with the cold pressor test. The maximum average systolic pressure after exercise in the hypertensive group rose 30 mm. above the ceiling reached when the cold test was used. The regular or usual systolic blood pressure in the hypertensive class was 28 mm. above the basal level as compared to 5 and 7 mm. in the low and normal groups.

TABLE V

History Findings for Subjects Observed in Blood Pressure Study

	H. B. P.*	N. B. P.*	L. B. P.*
Emotions			
Nervous and Excitable	43.7	11.7	14.3
Stable	54.0	56.3	85.7
H. B. P. in family	54.1	3.1	5.3
L. B. P. in family	0	2.3	17.8
Exercise			
Vigorous	6.2	6.2	7.1
Moderate	40.6	35.1	50.0
Mild	51.0	58.5	42.8
Quantity of food eaten			
Heavy eater	35.4	14.8	14.3
Medium eater	63.5	78.9	78.5
Light eater	1.1	6.2	7.1
Stimulants			
Coffee	12.5	11.7	28.5
Tobacco	16.6	19.5	50.0

* Indicates high blood pressure, normal blood pressure and low blood pressure, respectively. Figures in each vertical column represent the per cent of cases studied.

Some interesting information was obtained from the detailed history of these students (table 5). It was noted that 11.7 per cent of the normal, 14.3 per cent of the low pressure group, and 43.7 per cent of the hypertensive class presented evidence of being nervous or easily excited. Furthermore, 3.1 per cent of the normal and 5.3 per cent of the low blood pressure subjects and 54.1 per cent of the hypertensive group gave a history of familial hypertensive cardiovascular disease. The information obtained revealed that 17.8 per cent of the hypotensive class gave a family history of low blood pressure, whereas, none of the high blood pressure group and only 2.3 per cent of the normal subjects indicated any such disturbance among members of their immediate family or preceding generation. In the series of cases observed by Hines and Brown,[3] five times as many patients who had high blood pressure gave a positive family history of hypertensive cardiovascular disease as did subjects with normal blood pressure. This investigation not only confirms their results, but also indicates that there is a marked tendency for essential hypotension to be familial. There appears to be a definite hereditary pattern for blood pressure reaction. Perhaps this depends for the most part

upon some structural or physiological phenomenon of the autonomic nervous system, or endocrine function, or a combination of these factors, which are passed through the germ plasm from one generation to the next. There were 35.4 per cent of those students in the high pressure group who were heavy eaters, as compared to 14.8 and 14.3 per cent of the normal and low pressure subjects. As shown by the same table, it would appear that the amount of exercise or work is of little importance as a causative factor in the production of essential hypertension.

TABLE VI

Results of Reëxamination of Students with Abnormal Systolic Blood Pressure upon Entrance Physical Examination

Blood Pressure	Above 150 Mm. Hg Upon Entrance		Below 104 Mm. Hg Upon Entrance	
	No. of Students	Per Cent of Students	No. of Students	Per Cent of Students
Remained unchanged	96	24.8	56	17.6
To normal at 1st recheck	251	64.8	192	60.5
To normal at 2d recheck	25	6.4	69	21.7
To normal at 3d recheck	15	3.9	0	0
Total rechecked	387		317	
Not rechecked	132	25.4	74	18.9
Total	519		391	

To classify a patient as a hypertensive case after one blood pressure test cannot be condemned too strongly. The fallacy of so doing can be understood by the results obtained in our study (table 6). Note that the blood pressure of 64.8 per cent of the students with a systolic pressure above 150 mm. at the time of their entrance physical examination was normal at the time of the first recheck. After a third observation, 75 per cent were well within normal limits. Certainly, the excitement, nervousness, sense of uncertainty, new environmental adjustments, or other psychological effects must have been the etiological factors in producing most of these high systolic pressure readings. Riesman [4] and Grollman [5] have shown that such factors affect blood pressure. Just how this action occurs is still a matter of conjecture. Is it due to stimulation of the endocrine glands? Is it due to the autonomic nervous system alone with a resultant spastic constriction of the arterioles from psychic stimulation? Or can it be explained by the intrinsic myogenic capacity for the contraction and dilatation of the blood vessels? When the hypotensive subjects returned for their recheck, 82.2 per cent were within normal limits.

The autonomic nervous system is in a state of balance in normal persons under normal conditions. When the sympathetics and parasympathetics are in a state of equilibrium, a normal blood pressure results. When this balance is disturbed and more impulses are sent over the vasopressor or vasodepressor fibers respectively a hypertensive or hypotensive state ensues.

Whether or not this regulation is governed or determined by the carotid sinus, or initiated through the neurogenic arc, or by an intrinsic myogenic factor or unknown regulatory centers, or a combination of these factors has not been conclusively proved. The vasopressor effect of certain hormonal secretions, particularly adrenalin, is well known. Zipf [6] and Goerner and Haley [7] have produced some evidence that depressor substances may also be present in the body fluids.

Summary

Students were divided into high, normal, and low blood pressure groups, a careful history taken on each, and the blood pressure reactions to a standard exercise test were recorded.

1. The increase in the systolic blood pressure following exercise was greatest in the high blood pressure group.
2. The systolic pressure after exercise in the hypertensive and hypotensive classes returned to normal more slowly than did the normal group.
3. The diastolic pressure during exercise fell on the average about as far below the basal level as the diastolic rose above the basal level with the cold test. This pressure returned to the original level somewhat more slowly in the hypertensive group.
4. There was a far greater difference between the usual or regular systolic blood pressure and the basal blood pressure in the hypertensive class than between those levels in the normal and low pressure groups. This criterion is a definite aid in discovering those cases in which the blood pressure should be checked more frequently.
5. The pulse rate following exercise returned to the basal rate within two minutes in the normal and low pressure subjects.
6. Vasomotor response from other factors plays a more important rôle in causing a systolic increase in blood pressure during exercise than does the pulse rate.
7. The same factors which govern the emotional status of an individual play an important part in the blood pressure reaction.
8. There is a definite hereditary factor in the regulation of blood pressure. The tendency toward essential high or low blood pressure is carried by the germ plasm from one generation to the next.
9. The amount of work or exercise apparently is not an etiological factor in the production of essential hypertensive blood pressure.
10. The quantity of food intake may be an etiological factor in producing high blood pressure, since there were two and one half times as many heavy consumers of food in this class as in either of the other groups.
11. At least two or three subsequent rechecks should be made before a person is classified into the hypertensive or hypotensive group. This will prevent worry and anxiety in certain patients, and will be of considerable value to the physician in arriving at a correct diagnosis.

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THE TREATMENT OF ILLNESS OF EMOTIONAL ORIGIN BY THE INTERNIST *

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Between the small number of obviously psychotic people whom an internist sees and the larger number of patients who are sick solely because of organic disease are a vast number of sick people who are not "out of their minds" and yet who do not have any definite bodily disease to account for their illness.

It is reliably estimated that about one-third of the patients who consult the internist fall into this group. These are the so-called purely functional problems of medical practice. Approximately another third of the patients who consult an internist seem to have symptoms that are in part dependent upon emotional factors even though organic findings are present. The latter group is even more important than the first from the standpoint of diagnosis and treatment. These psychosomatic problems are often very complicated and because serious organic disease may be present the psychic factor is capable of doing more damage than in the first group. For example, while the neurotic with a normal heart may suffer a great deal subjectively and may even have a disturbance of the cardiac function, marked by various forms of arrhythmia, the heart, certainly in the majority of such patients, remains structurally healthy. But the neurotic patient who has organic heart disease may add a real burden to the work of his heart either through constant tension of psychic origin or more especially by means of acute episodes of psychic origin and thus may hasten a cardiac breakdown which, without psychic stress, in many cases might be indefinitely postponed.

The figures that I cite will differ, of course, depending upon the psychosomatic training of the observer, but those that I have given are average figures and are now widely accepted. If, for example, the internist is a diehard organicist who believes that every illness has an organic basis which will show up sooner or later "if studies are only thorough enough," the figures given by such an observer will differ from those of the psychosomatically trained physician who establishes the diagnosis of a functional disorder not simply on the basis of exclusion of organic disease but on positive findings from personality study as well. The latter recognizes that neurosis has its own distinctive features to be discovered by a study of the emotional life and that only in this way can serious errors in diagnosis and treatment be avoided. In this connection let me again emphasize that just as we cannot limit ourselves simply to the exclusion of organic disease in dealing with the purely functional group, so even more importantly in the second group is there the necessity for not resting content with the finding of an organic

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lesion. The day is near at hand for the final outmoding of the *either-or concept* (either functional or organic) in diagnosis and to place in its stead the idea of how much of one and how much of the other, that is, how much of the problem is functional and how much is organic. This is truly the psychosomatic concept in medicine.

To dispose of the first question that is often asked in such a discussion as this one—should the internist treat illness of emotional origin?—the answer is that he must. The problems are so numerous in his practice and the interrelationships of psyche and soma are so intimate and often so indissoluble, that he cannot avoid them. The question is whether by recognizing the important part that they play and by giving them more attention we can do a better job.

Present Treatment

When we review our present treatment of these patients we find that the first group are commonly told that no organic disease is present, that the whole thing is "functional" and are often dismissed without further care only to land eventually in the hands of some irregular practitioner or quack healer. Certainly in dealing with many of these patients, it is necessary to do more than assure the patient of the absence of physical disease. We will come back to this point later.

Worse than this the physician sometimes takes the attitude that the illness is imaginary, or that the patient is malingering, or assumes in some vague way that the patient is deliberately responsible for the illness. He refers to such patients slightingly as neurotics or lumps them all together as neurasthenics. I do not suppose it is necessary to remind this audience that these illnesses are just as real as cancer and that in no sense do they represent malingering. Before we can accomplish very much in this field we must do two things: one, correct our own attitude toward these illnesses so that we can take away from people the feeling that it is reprehensible to have an illness of emotional origin; and two, we must educate ourselves so that we can apply the same precise terminology to illness of emotional origin that we have, for example, in cardiac disease. It was only with more exact nomenclature that we made rapid advance in the cardiac field and the same will be true in the psychosomatic field.

Sometimes the patient is told that the physician does not *think* that anything is the matter but suspicion is cast upon some organ or system which needs watching and care. For example, the patient with symptoms referred to the heart region is told that his heart is all right but nevertheless he is cautioned to rest, medicine is given, and each time that he visits the physician his heart is examined again. We will consider this point later, but here it may be emphasized that in dealing with the majority of functional problems we must examine thoroughly, satisfy ourselves as to the absence of organic disease and then stop examining with the firm statement that "you do not have organic disease."

Very frequently following "thorough study" by means of the usual medical history, physical examination and laboratory investigation, some "pathological curiosity" is discovered which really has nothing to do with the illness and the patient is then treated as though organically diseased, is submitted to unnecessary medical or surgical treatment, which, in many instances intensifies the neurotic condition.

When emotional factors are associated with actual organic disease too little attention is paid to the emotional factors. The feeling exists and the statement is made that "the physical findings are sufficient to account for the illness." Again there are many physicians who pay lip-service to the question of psychic factors in illness by referring to the study and treatment "of the patient as a whole." They feel that they have done their duty to the study of the emotional life if they ask the patient if he is worried about anything and receive a negative reply. The point will be considered later that the patient is sick just because he is not aware of the things that are disturbing him. In other words the psychic material is forceful just because it is unconscious and is seeking another mode of expression. These are the same physicians who are apt to remark "but he doesn't look neurotic," perhaps believing that such a patient should by his general apprehension or by evidences of physical nervousness, betray the fact that he is neurotic. Unfortunately, most neurotics do not show any evidence of neurosis in their appearance, nor is the approach to their emotional problem so simple that the direct question—"are you worried about anything"?—will produce material of importance.

Emotional Problems

We know that these patients have been badly handled. Can we do any better? What is the matter with them and how should they be treated? Before attempting to answer these questions, let me quote from a letter received from an internist with whom I had some correspondence on this subject: "it seems to me extremely doubtful if education of the doctor along these lines is the answer to the problem. To delve into the personality of the patients who need this sort of study requires much more time, tact and patience than most practitioners have and we cannot refer any considerable number to psychiatrists. Furthermore, as you know, the accessibility of these facts varies very often with the intelligence of the patient. Even when the emotional set-up has been deciphered, you will have to admit that you would find very much the same impasse if you were up against the same situation yourself. In other words, while some doctors may be able to analyze these neurotic factors, generally speaking very few can alter them. And it has been my experience that understanding a situation is not always tantamount to solving it." I know you will agree that these are important questions and I shall try to answer some of them.

First of all let me say that these patients are suffering from disturbances

in their emotional lives; that is, the illness is of psychological origin and can be satisfactorily studied and treated only from a psychological standpoint. It is true that the ill health arises from long standing dissatisfactions in the business, social or home life of the individual and that this failure of adjustment to environment is manifested by a disturbance in some part of the personality, either as bodily symptoms of various kinds, capable of mimicking almost any disease, or as affections of the spirit resulting in attacks of anxiety, obsessions, phobias, depression and other disturbances of mood. What is not so generally realized is that the mere discovery of the so-called dissatisfactions or unpleasant occurrences in the life situation of the individual is not a sufficient explanation nor even an adequate indication of the psychic background of the illness. In other words, besides excluding organic disease and besides the effort to tie up the occurrence of an unpleasant episode and the beginning of the illness from the standpoint of a time relationship, it is of the greatest importance to know the patient's ability to adjust to such situations, his pattern of reaching to them, the degree of anxiety in his make-up, the nature and seriousness of his conflicts. Personality study is necessary if we are to establish a specific relationship of the psychic situation to the personality of the individual. Just as the typhoid bacillus is specific for typhoid fever, depending of course upon the susceptibility of the individual, so the psychic event must be specific for the personality structure of the person. To make such studies one must have some training in psychopathology. When psychopathology is given an equal place with tissue pathology in our medical curriculum and is as well taught we will finally realize that psychotherapy is an integral part of our medical discipline.

Psychosomatic Study in Illness

Can any advice be given as to how to proceed with this kind of a study? In a general way it may be stated that in addition to the physical study it consists simply in getting to know the patient as a human being rather than only as a medical case. Too often, as already stated, the patient is looked upon as a physiological mechanism and is studied by means of medical history and physical examination aided by "instruments of precision" and chemical tests. Tape measures and test tubes carry the erroneous notion of exactness and thoroughness—erroneous because the emotional life of the individual, which may hold the key to the solution of the problem, is not investigated or at best inadequately so.

Probably the best way to deal with these patients is first to satisfy ourselves and establish their confidence by a thorough medical history which must contain more information regarding the family and social background of the patient than our present histories do; then a complete physical examination and such laboratory tests as are necessary to exclude organic disease or to establish the precise nature of the organic problem and the amount of disability which it in itself is capable of causing. Having as-

sured the patient that no physical disease is present in the first instance, or that it is present to a certain extent in the second group, but that *the disability is out of proportion to the disease*, it is usually easy by examples of psychic causes for such physiologic disturbances as blushing, gooseflesh, palpitation, diarrhea, etc., to make the patient understand that a disturbance in his emotional life may be responsible for the symptoms. Then important clues for this disturbance can usually be found by encouraging a discussion of problems centering around vocational, religious, marital and parent-child relationships. This is usually best accomplished indirectly rather than by direct questions. The more one can persuade such a patient to talk about "his other troubles" the sooner do we come to an understanding of "the present trouble." The greater our success in switching the conversation from symptoms to personal affairs, the sooner do we come into possession of the real problem disturbing the patient. We are all familiar with the patient who is preoccupied with his bowel function and wants to talk about nothing else, whose whole life really seems to surround his daily bowel movement. It is the physician's duty tactfully to switch him from a discussion of his symptoms to a discussion of his personal life. It is not necessary to inform the patient that he is undergoing psychological treatment. Simply get him to talk about himself as a person rather than as a medical case. In adults domestic problems and professional and business relationships play a large part in functional illness. In young, unmarried people, family relationships, choice of a career, and often religious and sexual problems are important topics for discussion.

Organ Language

A method of helping patients to understand their symptoms which I find useful is based upon the symbolism of symptoms. I often say to them that if they cannot find an outlet for tension of emotional origin by word or action, the body will find a means of expressing this tension through a kind of "organ language." For example, if a patient cannot swallow satisfactorily and no organic cause can be found, it may mean there is something in the life situation of the patient that he "cannot swallow." Nausea in the absence of organic disease sometimes means that the patient "cannot stomach" this or that environmental factor. Frequently a feeling of chest oppression accompanied by sighing respirations, again in the absence of organic findings, indicates that the patient has a "load on his chest" that he would like to get rid of by talking about his problems. The patient who has lost his appetite and as a consequence has become severely undernourished, the so-called anorexia nervosa, which in its minor manifestations is such a common problem, is very often emotionally starved just as he is physically starved. The common symptom fatigue is very often due to emotional conflict which uses up so much energy that little is left for other purposes. Again emotional tension of unconscious origin frequently ex-

presses itself as muscle tension giving rise to aches and pains and, sometimes, these are represented by sharp pains such as atypical neuralgias. An ache in the arm sometimes means that the patient would like to strike someone, but is prevented from doing so by the affection or respect that is mingled with his hostility, rather than representing the response to a focus of infection. May I suggest that the next time you deal with an atypical neuralgia of arm or face you look for " focal conflict " as well as " focal infection." Itching for which no physical cause is found very often represents dissatisfaction with the environment which the individual takes out upon himself; martyr-like he scratches himself instead of someone else. "All gone" feelings in the epigastrium, " shaky legs," even vertigo are common physical expressions of anxiety and the anxiety attack, so frequently called a " heart attack," gall-bladder disturbance, hyperthyroidism, neurocirculatory asthenia, hyper-insulinism, etc., is still far from being understood in general clinical medicine in spite of the fact that Freud described it more than 40 years ago. I would like to give many more examples and cite illustrative cases but time does not permit. Only one more point before concluding this part of the discussion and that is that the gastrointestinal tract is above all other systems the pathway through which emotions are often expressed in behavior. As has been well said, the abdomen is the sounding board of the emotions. And certainly it is not very difficult to understand why this should be so. In early life the infant derives emotional satisfaction as well as sustenance from his feeding. Feelings of affection and anger get bound up with the feeding process and these associations may become deeply buried in the mental life of the individual but are never lost. If then the need for food and need for affection are indissolubly bound in the unconscious emotional life of the patient, we are certain to see a great many individuals who on the surface are grown up adults but who underneath express by means of the stomach their infantile desire for love and affection. Then frustration in real life frequently results in disturbances of muscle tension and secretion to provide the background for functional gastrointestinal disturbances.

This whole approach can be summed up in the following fashion: *if symptoms exist without an organic basis or, if organic disease fails to explain the symptoms completely, look for their meaning from the standpoint of behavior.*

Such an approach can be applied to a wide variety of symptoms and can be utilized very generally in talking with patients. Nor does it require a very high degree of intelligence on the part of the patient to follow this simple explanation. Patients in the clinic as well as those in the private ward can be dealt with in this fashion and as you well know are just as susceptible to these functional disorders.

Sexual Factors

This is too large a subject to cover in a short paper, but one point of special importance does deserve consideration and that is the relation of

sexuality to neuroses. Ever since the introduction of the epoch-making studies of Freud to the problems of neurosis, medicine has misunderstood his conception of sexuality. He has often been quoted to the effect that disturbances in genital activity are the sole cause of the neuroses. This is quite far from the truth. It is rather that difficulty in the sexual sphere appears as a revealing index to a neurotic personality and can be looked upon in that light. In other words, in much the same manner that urea retention serves as an index to an impending uremia, so do disturbances in the sexual life of the individual, such as varying degrees of frigidity in the female and varying degrees of impotence in the male, serve as a reliable index to the kind of a personality that is very liable to develop a neurosis. Here again, I must advise you to steer the conversation by means of indirect questioning and to listen rather than talk. This is especially important in regard to sexual problems and the more experience I have with patients the less I find it necessary to question them directly regarding these intimate matters. Sexual difficulties are rarely in themselves the cause of the kind of illness we have been considering; when they are important and the patient has a satisfactory relationship to the physician, sufficient confidence will eventually be gained to permit discussion of these intimate matters. In women questions regarding menstruation and child-bearing will often lead naturally to such a discussion.

In this connection let me suggest a cautious attitude in regard to marital maladjustments out of which situations symptoms often arise. The better these problems are understood from the standpoint of personality study the clearer it becomes that serious emotional maladjustment often stands behind the marital problem. Consequently casually to give advice regarding marriage and childbearing, divorce and extra-marital relationships as short cuts to involved emotional problems is to assume knowledge beyond present human understanding.

Psychotherapy

And now to come back to one of the questions raised by the internist who wrote to me regarding these matters, " suppose you do find something of importance in the emotional life of a patient, some conflict that is causing illness, what can you do about it? What good does it do the patient to know?" First of all, it is often a great help to the patient to know that the ailment is not organic in origin but is due to a disturbance in his emotional life. When a neurotic symptom is divorced from a fear of organic disease, cancer for example, it loses its force and then the slogan " carry on in spite of symptoms," often helps the patient a great deal. This is especially true if the psychological approach that I have discussed is combined with the study and the emotional background of the illness is made clear to the patient. This brings us to the question—" what then is psychotherapy?" Too often it is assumed to be something vaguely referred to as " the appli-

cation of the art of medicine." This defies analysis but seems to represent a combination of the experience and common sense of the seasoned practitioner, an intuitive knowledge of people plus the cultivation of a charming bedside manner, such trifles as serving food in attractive dishes, and the generous use of reassurance. The psychological approach in medicine, essential for psychotherapy, consists of something more. It is a medical discipline to an equal degree with internal medicine itself. It is an effort to understand the personality structure of patients, the mental mechanisms which are at work, and the specific relationship of psychological situations in the precipitation of the illness.

Reassurance in the majority of instances, unless combined with an analysis of the illness from the standpoint of the behavior, gives only temporary help and depending upon the degree of anxiety has to be constantly repeated, like a dose of digitalis in a failing heart. Closely allied to reassurance is another superficial treatment that rarely results in more than temporary help, i.e. environmental manipulation without any attempt to give the patient insight into his conflicts. Real psychotherapy, which is directly the opposite of simple reassurance, tries to make the patient understand the meaning of his symptoms and the nature of his conflicts. It is a reëducational process and when properly done leads to sufficient emotional development so that the necessity for symptom formation is abolished. The best example of this kind of psychotherapy is psychoanalysis, but for various reasons this method cannot be applied directly to the majority of patients. Nevertheless, psychoanalytic insight and guidance in management combined with reëducation and reassurance prove adequate for the majority of functional disturbances. Between simple reassurance at one end of the scale and adequate psychoanalysis at the other, there are all degrees of psychotherapy which can be applied depending upon the degree of illness and the circumstances of the patient. It is my contention that every physician should be trained in psychological medicine so that he may be able to understand and manage the many emotional problems that are presented to him daily. In addition I think some internists will adopt psychosomatic medicine as a subspecialty in the same way that others interest themselves chiefly in cardiology, gastroenterology, etc.

As my correspondent stated, a considerable number of these patients cannot be sent to psychiatrists. Nor is it necessary. Another way of stating the problem is to say that there is major and minor psychotherapy just as there is major and minor surgery. Many physicians who practice general medicine feel themselves capable of doing minor surgery, but only a few have the skill to attempt major surgery. They would not permit themselves to attempt something for which they are not prepared. This is just as true in regard to psychotherapy. The general physician must be able to treat the minor ailments but he must be able also to recognize when the problem is beyond him and then refer the patient elsewhere for major psychotherapy.

Such knowledge and such an approach will frequently save the patient from unnecessary, troublesome and expensive medical or surgical treatment with a resulting further degree of invalidism.

At this point let us consider some of these principles as applied to a psychosomatic problem. I think this can best be done by citing an illustrative case.

Case Report

A white man, aged 37, first seen in March 1938, complained of "a heart condition," insomnia, tiredness and dizziness, inability to relax, rapid heart action, missed beats and sweating, and, according to the physician who referred him, suicidal tendencies.

The heart murmur had been discovered in school at the age of 12. He does not recall that any particular attention was paid to it at this time but in high school he was taken off of the ball team because of "an athletic heart." Thus he grew up with the idea that there was something seriously wrong with his heart.

At the age of 29, while swimming in an indoor pool, he had a sudden attack of palpitation, which was called a "heart attack" by his physician, and several days of complete bed rest were advised. On two subsequent occasions he also had the same kind of an attack; one attack terminated in a vomiting seizure. The other symptoms mentioned above have also been present since that time. He has seen many doctors, has considerably limited his activities and, according to his statement, has not wanted to marry because of his heart condition.

Just before coming to me he had suffered much from insomnia and at lunch the day before he had had rapid heart action and sweating, had felt dizzy and faint, and had a very heavy feeling in his chest. He had been nervous and jittery since. He became so desperate that he threatened suicide.

The physical examination showed a robust white man with perhaps slight cyanosis of the lips but no dyspnea and no clubbing or jaundice. The heart action was forceful. There was slight scoliosis which was responsible for slight displacement of the heart to the left; the organ did not seem enlarged. The sounds were well heard and seemed normal except for a slight systolic murmur in the third left interspace. There was no thrill. The remainder of the physical examination was negative.

Ordinary laboratory studies were within normal limits. There was no evidence of impairment of cardiac function and the response to effort was normal. I concluded that we were dealing with a congenital lesion, probably ductus arteriosus, which had not affected the working of the heart.

In 1934 and again in 1936 the patient was studied by Dr. Hugo Roesler to whom I am obliged for permitting me to use the following notes:

"1934. Mild cyanosis of the lips. Heart not enlarged. The apex is rather diffuse and a double wave short systolic retraction is noted. The first apical sound is split; no thrill. In the third left intercostal space there is a low, soft, deep-seated systolic murmur. The pulmonic second sound is hardly audible. The murmur is not influenced by respiration. Blood pressure systolic 138, diastolic 95. Rate 80 per minute. "Roentgen-ray. The heart is normal in size; there is moderate prominence and increased systolic pulsation of the pulmonic arc.

"Electrocardiogram: Regular sinus rhythm; normal auriculoventricular conduction time. Moderate slurring of the initial deflection in Leads II and III. The T-waves are positive in all three leads. A Q-wave is present in Lead III.

"Discussion. Congenital cardiovascular malformation, most probably patency of the ductus arteriosus; other malformations may be present but cannot be proved. The patient has had attacks of either sinus or auricular tachycardia and also attacks of what seemed to be auricular fibrillation. But these disturbances are not in connection with the anatomical malformation. There is no evidence of disease or dysfunction of the myocardium. Personality study is advised.

"1936. General findings, fluoroscopy and electrocardiogram unchanged. Blood pressure standing 120/60; recumbent 130/80. Conclusions as before."

Life Situation

The patient was the next to the youngest in a family of nine children. His mother had died at the age of 47, when the patient was 13, of some "kidney condition"; she had been sick for years. The father shortly had married again and the patient now makes his home with the aged father and step-mother; all of the siblings have married and live away from home.

A short time before the patient became ill the father had had a stroke of apoplexy and had been a cripple but not an invalid since. He is now 72 and has high blood pressure. The patient supports his father and step-mother, receiving no help from the rest of the family, which he very much resents although he does not readily admit it. Conversations regarding his inability to marry indicate that not only his heart condition but the fact that he is responsible for the care of his sick father and step-mother is a deterrent; in other words he feels that he is sacrificing himself for his invalid father.

Another circumstance that seemed important was that following his father's stroke and just before the patient's first "heart attack" a man had been suddenly killed at his place of business and he felt that he had given the order to this man which resulted in his being in a certain spot at the moment that the accident occurred which resulted in his death. He could not forgive himself "for sending this man to his death" although it was obvious that it was a routine order in the ordinary conduct of the business. Nevertheless, guilt and self-accusation persisted. Further study which I shall not detail here indicated that this episode had reminded him of his father's stroke and had energized a psychic conflict in regard to his father, for it became clear that the excessive solicitude for his father covered unconscious hostility and fancied threats to his father's welfare awakened great anxiety in the patient. Anxiety not only disturbed his heart action but resulted in insomnia and excessive urination as well.

When disturbed "his chest (heart) would feel solid, heavy and hot; the left arm would ache and feel numb, the left hand was cold; the head felt swollen, the hair stood on end, he would drool saliva and urinate large quantities at frequent intervals." These were clearly the symptoms and signs of his pronounced anxiety. Insomnia seemed to disturb his efficiency as much as the concern over his heart. His attitude was a determination to go to sleep which, of course, resulted in just the opposite effect. He gave the impression of being not only a vigorous but a violent person with no outlet for his aggression. Thus he would dream a great deal about fighting and became much disturbed in witnessing athletic contests. When he visited my office he would stomp in and jerk the office chair before seating himself.

A symptom to which he apparently paid little attention but which was significant as a further indication of his neurotic difficulties was impotence which he said came on gradually shortly after he became ill. It was obviously of psychological origin because the physical examination was negative and the impotence would assert itself only at certain times and with certain women.

I explained to the patient that he had a congenital lesion of the heart that in no way inconvenienced the working of that organ and I assured him that his symptoms had nothing to do with this "pathological curiosity." Gradually I succeeded in convincing him that his heart was not seriously diseased, that he was able to engage in many activities that he had denied himself, and that no harm would come to his heart as a result. The anxiety attacks became less intense and came at greater intervals and his sleeping was much improved. Occasionally an attack would occur and when it did all of his doubts regarding his heart would return. This would necessitate further reassurance along the lines already indicated. At the same time an effort was made to show the patient some of the psychic reasons for his illness. Attacks would frequently occur when family situations arose which stirred up his aggression. Because of this throttled aggression he was checkmated in all directions. His solicitude for his father and step-mother would not permit him to express any indignation to them or to his brothers. He was afraid to work hard or to engage in any athletic activities because of his heart, and even his sexual function was impaired. Hence it was obvious that we were dealing with a severely inhibited individual whose normal aggression could find no outlet. Nevertheless, as he gained confidence from reassurance and some insight into the emotional background of his illness he became a more effective and more contented person, engaged in longer hours of harder work and indulged himself in other regards.

However, his attention had been so fixed upon his heart that the slightest recurrence of symptoms would bring some of his old doubts back again. Once more reassurance, like a dose of medicine, would improve his condition. The advice of physicians to rest and to limit his activities had played into his unconscious need for illness. Just the opposite kind of tactics, teaching him to ignore his heart so far as it was possible for him to do so, to carry on his activities in spite of symptoms, together with the effort to show a relationship between his attacks and his emotional life resulted in a considerable degree of improved health and happiness so that he became more efficient in his work and more effective in his social contacts.

Cost of Psychotherapy

Now we come to the question of time, effort and the expense of psychotherapy. Certainly it is true that all of this takes time and effort and must be paid for, yet when we look into the time, effort and expense that have been expended by many patients or by institutions taking care of these patients in the usual medical approach, we realize that an hour or two well spent in a discussion of the life situation of such patients would obviate a great deal of this other expense. In the outpatient medical department we are making a study of patients of this kind, the criterion for selection being a chart one inch thick. It is amazing what the total expense of a great many of these unnecessary studies amounts to so far as the institution is concerned, and of course the same thing is true in the case of private patients. I think the day is close at hand when we will regard some of these thick-chart patients, this poly-physical approach, with the same amusement and disdain with which we now regard the polypharmacy of a bygone age in medicine. Hospitals are beginning to understand that it is not only intelligent but economical to utilize the service of a psychiatrist in the general medical division and this same idea could be applied with great benefit to the much discussed medical insurance plans.

The last hundred years in medicine have seen the structural concept of disease lead from morbid anatomy and cellular pathology to the bacteriological era and its great discoveries. Then came the period of biochemistry and metabolism which has led to the enormously productive endocrinology. We are just tapping the door leading to the era of psychological medicine which I am confident will make contributions of equal importance.

Medicine had its real beginning in the study of man at the dissecting table. Let us continue with the study of man not only as an anatomical and physiological mechanism but as a human being possessed of loves and hates, urges and passions capable of disturbing his soul and his body.

HEMATOLOGIC ASPECTS OF SPACE CONSUMING LESIONS OF THE BONE MARROW (MYELOPHTHISIC ANEMIA)*

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In the medical literature of recent years attention has been called to a type of anemia usually associated with immature red and white cells in the peripheral blood. This anemia has been described under such titles as myelophthisic anemia,[1] leuko-erythroblastic anemia,[2, 3] myelosclerosis associated with a leukemoid blood picture,[4] megakaryocytic myelosis with osteosclerosis,[5] and, simply, a leukemoid reaction.[6] The data reported in the various cases so described suggest that the underlying structural changes of the marrow were essentially sclerotic in character.

During the past several years a large number of patients with anemia have been examined at the University of California Hospital whose blood streams contained abnormal cells and whose clinical pictures presented difficult diagnostic problems. In the course of the study of a group of these patients, it was observed that the hematologic data were similar. On biopsy of the sternum a varied pathologic change was found but the patients had in common a marrow replaced by abnormal tissue. Because of the difficulties encountered in the diagnosis of the conditions causing replacement of marrow, the paucity of hematologic data in the literature and the confusion arising from their classification, the hematologic aspects of space consuming lesions of the bone marrow are discussed in this paper.

Method of Examining the Bone Marrow

Under local anesthesia an incision was made through the skin and subcutaneous tissues. A " button " of bone having a diameter of 15 mm. was removed with a trephine. Specimens of marrow were removed with a curette and spread preparations were made immediately on cover slips. These were stained according to the method of Wright or Giemsa. Other pieces of marrow tissue were fixed in Zenker's fluid containing 5 per cent glacial acetic acid and at the appropriate time were embedded in paraffin, sectioned and stained with hematoxylin and eosin.

Report of Cases

Generalized Osteosclerosis, Amyloid Disease of Liver and Kidneys, Tertiary Syphilis

Case 1. A. P., a white man, aged 50, was admitted to the University of California Hospital on August 23, 1938, complaining of weakness and dyspnea. Because

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of anemia he had been given a transfusion of whole blood by his physician on January 17. This procedure had been repeated on March 15, May 17 and June 9. On June 10 a laparotomy had been performed for the purpose of examining the abdominal contents. The operator had noted that the liver was moderately enlarged and smooth, and appeared normal in color and consistency; the spleen was normal in size; the lymph nodes were not apparently enlarged; no tumor masses could be felt along the course of the gastrointestinal tract; and no stones were palpable in the gall-bladder. Despite the administration of transfusions, liver extract potent in pernicious anemia, large doses of iron and various vitamin preparations, the patient had continued to be anemic.

Physical Examination. On admission to the hospital the patient appeared very thin and emaciated. The lymph nodes were not abnormally enlarged. The teeth were carious and the margins of the gums showed evidence of infection. The heart was not enlarged on percussion and no cardiac murmurs were heard. The blood pressure was 122 mm. mercury systolic and 95 mm. diastolic. The abdomen was moderately protuberant and a smooth mass with a firm non-tender edge could be felt which extended 10 cm. below the right costal margin, 12 cm. below the xiphoid process and 4 cm. below the left costal margin. No other masses could be felt.

Laboratory Data. The blood count showed: erythrocytes 2,268,000 per cubic millimeter; hemoglobin 44 per cent (6.1 gm.) Sahli. The mean corpuscular volume was 97 cubic microns, the mean corpuscular hemoglobin concentration was 21 per cent and the mean corpuscular hemoglobin was 20 micrograms. The color index was 0.77. The leukocytes were 14,100 per cubic millimeter. The differential count showed: segmented leukocytes 61 per cent; non-segmented leukocytes 19 per cent; large lymphocytes 5 per cent; small lymphocytes 10 per cent; monocytes 3 per cent; myelocytes 2 per cent. The reticulocytes were 1.6 per cent. The platelets were 205,000 per cubic millimeter. The icterus index was 2 units. The urine contained a large amount of albumin but showed no evidence of a reducing substance with Benedict's reagent. The tuberculin test gave negative reactions to both human and bovine antigens in dilutions of 1 to 1000. The Mosenthal dilution and concentration test of kidney function showed a variation of only 0.002. The intravenous injection of phenolsulphonphthalein resulted in 68 per cent excretion in two hours. The blood Wassermann test was reported 4 plus positive; the Kahn test was also strongly positive. The spinal fluid Wassermann test was negative. Tests for amyloid disease with the dye congo red showed 100 per cent absorption in 1 hour. A test for liver function with bengol rose showed 50 per cent retention in 8 minutes and 23 per cent at 16 minutes (normal range). The total blood serum protein was 6.09 of which 1.34 was albumin and 4.75 was globulin; the albumin-globulin ratio was 0.28. Fluoroscopic examination and roentgenograms of the gastrointestinal tract failed to show any abnormalities. Roentgenograms of the right femur and the left humerus demonstrated an advanced osteosclerotic process in the marrow cavities. Films of the skull showed a similar process involving the cranial bones, the facial bones and the maxillae. According to a film of the chest, the heart, aorta and lung fields were within normal limits. The blood serum calcium was 10.28 mg. per 100 c.c. and the phosphorus was 22.02 mg. per 100 c.c. The basal metabolic rate was 14 per cent plus. A biopsy of the sternum was done and a button of bone 15 mm. in diameter was removed. There was no evidence of marrow cavity. Specimens of bone were fixed in Zenker's solution, decalcified, sectioned and stained with hematoxylin and eosin. Examination under the microscope showed a complete absence of the usual architecture of the bone marrow. The bone elements were greatly in excess of normal. There was evidence of slight erythropoiesis and much fibrosis between the spicules of bone. A few young forms of the white cell series were found. Diagnosis: Sternal bone marrow showing osteosclerotic changes and hypoplasia of erythropoiesis and myelopoiesis.

Course of Illness. Treatment consisted of the oral administration of a saturated solution of potassium iodide and the parenteral administration of bismuth salicylate in doses of 0.2 gm. at weekly intervals. While in the hospital the patient gained 2 kg. in weight, but there was little change in the red blood cell or hemoglobin values or in the size of the liver.

Gaucher's Disease with Splenomegaly and Replacement of Bone Marrow with Kerasin Cells

Case 2. E. F., a Jewish female, aged 54 years, was first seen on January 3, 1935. For two years she had been under the care of her family physician because of precordial pain, dyspnea and a generally enlarged abdomen. The attacks of pain had been relieved quickly with nitroglycerin.

Physical Examination. The patient appeared anxious and emaciated. She became dyspneic with slight exertion and had cyanosis of the lips and of the tissue beneath the finger-nails. The skin was of a "dusky" hue. The superficial lymph nodes were not enlarged. The gums receded about many of the teeth and bleeding points appeared along the gingival margin upon slight trauma. The heart was found greatly enlarged on percussion and the apex was at the anterior axillary line in the fifth interspace. No cardiac murmurs could be heard. No râles were heard in the lungs. The blood pressure was 160 mm. of mercury systolic and 100 mm. diastolic. The abdomen protruded markedly and the skin was stretched tightly over it. A large smooth mass, presumably the spleen, was felt in the left side of the abdomen and extended into the pelvis and slightly to the right side of the mid-abdominal line. A second mass, presumably the liver, was felt on the right side of the abdomen, the edge reaching halfway between the umbilicus and the brim of the pelvis. There was pitting edema of ankles and feet.

Laboratory Data. On January 3, 1935, the blood count showed: hemoglobin 58 per cent (8.1 gm.) Sahli; erythrocytes 3,640,000; and leukocytes 1,300 per cubic millimeter. The differential count showed: segmented polymorphonuclear leukocytes 38 per cent; non-segmented leukocytes 23 per cent; polymorphonuclear basophiles 1 per cent; large lymphocytes 6 per cent; small lymphocytes 17 per cent; monocytes 10 per cent; myelocytes 4 per cent; 1 nucleated red blood cell per 100 white blood cells. The platelets were 90,000 per cubic millimeter. The volume of packed red blood cells was 24 mm.; the mean corpuscular volume was 79 cubic microns; the mean corpuscular hemoglobin concentration was 29 per cent; the mean corpuscular hemoglobin was 23 micrograms. There was marked poikilocytosis and anisocytosis of the erythrocytes.

Course of Illness. The patient remained under observation from January 1935 until June 1938. During this time the anemia and leukopenia persisted and the platelets varied from 30,000 to as high as 110,000. On occasions petechial hemorrhages appeared in the skin and blood oozed from the gums. In January 1938 the patient complained of constant pain in the region of the lower dorsal vertebrae. A roentgenogram of the spine showed collapse of the body of the ninth dorsal vertebra. The patient continued to have attacks of precordial pain and marked dyspnea with slight exertion. On June 8, 1938, during such an episode, she suddenly collapsed and expired.

Gross Postmortem Examination. The autopsy was performed by Dr. C. L. Connor. The body was that of a poorly developed, emaciated woman. The gums were swollen and evidences of small hemorrhages could be seen at the gingival margins of some of the teeth. On the right side of the face were several ecchymotic areas. The abdomen was tremendously distended. The legs were edematous and many petechial hemorrhages were present in the skin.

Internal organs: The abdominal cavity showed a smooth lining and contained about 1 liter of clear amber fluid. The left pleural cavity contained about 400 c.c. of clear fluid and the right about 300 c.c.

Heart: The pericardium was greatly distended and contained a tremendously enlarged heart which weighed 548 gm. There were 800 c.c. of clear fluid in the pericardial sac. The visceral pericardium showed several roughened, fibrotic areas on the anterior surface and the coronary arteries were quite prominent and heavily calcified. The mitral valve was thickened and its ring contained a calcified and apparently ossified deposit which projected beneath the posterior leaflet of the mitral valve.

Lungs: There was no evidence of any disease process in the lungs.

Liver: The liver was greatly enlarged and weighed 3,650 gm. The cut surface was of a dull red-brown color and showed a multitude of thin, gray streaks which were thought to represent an increased amount of portal connective tissue.

Spleen: the spleen was tremendously enlarged and weighed 4,400 gm. It occupied the entire left half of the abdomen and extended into the pelvis. There were no adhesions about the spleen but rounded nodules about 2 cm. in diameter could be seen bulging up under the capsule. The cut surface was deep red and friable. Throughout the pulp were a large number of poorly defined, slightly raised tumor masses, some of which showed evidence of hemorrhage while others were greenish-yellow to red in color.

Bone and bone marrow: The sternal, costal and vertebral bones were quite soft and easily cut with a knife. The marrow appeared to be replaced by a very soft red hyperplastic tissue surrounded by a greatly thinned cortex. In some areas the marrow content was of a greenish-yellow color. The bodies of the ninth and tenth dorsal vertebrae were completely collapsed.

Other organs: The gastrointestinal tract, pancreas, kidneys, aorta, thyroid and adrenals showed no abnormalities.

Microscopic Postmortem Examination. Spleen: The sinusoids were pitted with cylindrical masses of large cells and the splenic pulp was almost completely obliterated. The large cells contained relatively small, round nuclei. The cytoplasm was composed of a faintly staining reticular material which appeared to contain vacuoles. Specimens stained with phosphotungstic acid hematoxylin showed more definitely the fibrillary material running through the cytoplasm. This structure seemed characteristic of Gaucher's disease and the material in the cells was apparently kerasin. The few splenic follicles that could be seen were represented by a small number of scattered lymphocytes.

Liver: The liver presented a most peculiar picture of well advanced cirrhosis in which the islands of liver cells remained in a fibrous tissue stroma. The connective tissue appeared to be of loose structure and between the fibrils here and there the characteristic cells of the type described in the spleen were seen. Accumulations of similar cells could be seen beneath the capsule and in some of the sinusoids.

Kidneys: There were some scars beneath the capsule and in the subjacent cortex there were fibrosed glomeruli. The arterioles showed well marked thickening and degeneration of the type associated with hypertension.

Bone marrow: This was active to the extent of moderate hyperplasia in which the erythroblasts and normoblasts predominated. Myeloid cells and megakaryocytes were seen in moderate numbers. The normal structure of the marrow was disarranged by groups of cells containing kerasin similar to those described in the spleen and the liver. These cells appeared in greatest numbers beneath the cortex of the bone.

Pancreas: There was some increase of interstitial connective tissue and occasional kerasin-containing cells were seen.

Other organs: No Gaucher cells were seen in the lymph nodes. No significant abnormalities were noted in the adrenals, ovary, thyroid or breast tissue.

Postmortem Diagnosis: Gaucher's disease with kerasin-containing cells in the spleen, liver, bone marrow and pancreas. Cirrhosis of the liver. Splenomegaly.

Hypertrophy of the heart and myocardial degeneration, ossified annulus fibrosus of the mitral valve. Generalized arteriosclerosis.

Bone Marrow Showing Carcinomatous Metastasis (Surgically Removed Carcinoma of Breast 11 Years Prior to Hospital Entry). Splenomegaly

Case 3. I. A. P., a white American female, aged 58, entered the University of California Hospital on December 9, 1937, complaining of weakness, pallor, dyspnea and hemorrhages into the skin. She stated that 11 years previously her left breast had been removed because of carcinomatous degeneration. Since then frequent examination of the operative site by her physician and roentgenograms of the lungs had failed to reveal signs of local recurrence or metastatic foci in the lungs. Her symptoms began five months before entry when she first noted that she was easily fatigued. At that time her physician found that her hemoglobin was 40 per cent. Dyspnea, weakness and loss of weight had developed progressively since then.

Physical Examination. The patient appeared weak and emaciated. There was marked pallor of the skin and mucous membranes. An ecchymosis was present on the right forearm and petechial hemorrhages were seen in the skin of the lower extremities. Slight gingivitis was present, but there was no oozing of blood from the gums. The lymph nodes were slightly enlarged, particularly in the left axillary region. Moist râles scattered throughout the lungs could be heard on inspiration. A well healed operative scar was present in the left upper thorax and the left breast was missing. The heart was not enlarged on percussion but a systolic murmur was heard in the region of the apex. The abdomen was slightly protuberant. A firm, smooth mass with a notched border, presumably the spleen, was felt in the left upper quadrant of the abdomen. The liver was smooth and slightly tender and its edge was felt 3 cm. below the right costal margin.

Laboratory Data. The blood count showed: hemoglobin 23 per cent (3.3 mg.) Sahli; erythrocytes 1,770,000 per cubic millimeter; and leukocytes 5,400 per cubic millimeter. The differential count was: segmented polymorphonuclear leukocytes 30 per cent; non-segmented leukocytes 20 per cent; polymorphonuclear eosinophiles 2 per cent; lymphocytes 20 per cent; monocytes 1 per cent; myelocytes 19 per cent; normoblasts 30 per 100 white blood cells; platelets 25,000 per cubic millimeter. There were marked anisocytosis, poikilocytosis and polychromatophilia of the red blood cells. The mean corpuscular volume was 101 cubic microns and the mean corpuscular hemoglobin concentration was 32 per cent. Fluoroscopic examination of the chest revealed many lesions within the pulmonary parenchyma. Roentgenograms showed a highly advanced degree of a combination of osteolytic and osteoblastic new bone formation in the fourth and fifth lumbar vertebrae, in all the bones of the pelvis and in the upper six inches of the femur. Diagnosis was carcinomatous metastasis of the bones. The Wassermann and Kahn tests of the blood for syphilis gave negative reactions. Biopsy of sternal marrow: The marrow tissue was almost entirely replaced by wildly growing epithelial tissue accompanied by dense fibrous tissue. The epithelial cells were arranged in small sheets and groups; among these cells mitotic figures were seen. There were a few hematopoietic cells, mostly of the myeloid type. It was concluded that the sternal marrow showed carcinomatous metastasis.

Multiple Neurofibromatosis of Skin (Von Recklinghausen's Disease), Bone Marrow and Posterior Cranial Fossa

*Case 4.** T. B., a white American male, aged 39, entered the University of California Hospital on December 8, 1936, complaining of dizziness and headaches. He

* This case is to be reported in detail at a later date.

had been in the hospital on three previous occasions and the following diagnoses had been made: (1) multiple neurofibromatosis; (2) dorsal kyphosis; (3) possible myeloid leukemia. He believed that he had injured his spine when he fell from a wagon at the age of three years. The deformity of the spine had been evident since the age of 14. He had had small, painless, papillomatous nodules in his skin since childhood. His symptoms at time of entry had started about one month previously and since then he had been dizzy almost constantly. He had noted double vision on occasions and several times had had a tendency to fall toward the right while walking.

Physical Examination. The patient was of short stature, poorly developed but fairly well nourished. Scattered over the body were seen innumerable non-tender nodules in the skin varying in size from 2 mm. to 2 cm. These were slightly elevated and a few of them were pedunculated. The thoracic vertebrae showed marked kyphoscoliosis and the chest was considerably deformed. The heart was displaced slightly upward and centrally. A soft systolic murmur was heard at the mitral area. The tip of the spleen was felt 6 cm. below the left costal margin and the edge of the liver was felt in the right epigastrium. A neurological examination revealed nystagmus on the right, a tendency to fall to the right, a positive Romberg and possibly motor weakness of the third nerve.

Laboratory Data. The blood count showed that between the years 1932 and 1936 the erythrocytes varied from as low as 2,780,000 per cubic millimeter to as high as 4,840,000 per cubic millimeter; the hemoglobin varied from 60 to 80 per cent (8.2 to 11 gm.) Sahli; and the leukocytes varied from 3,450 to 15,500 per cubic millimeter. The platelets were 180,000 per cubic millimeter. A typical differential count showed: segmented polymorphonuclear leukocytes 51 per cent; non-segmented leukocytes 21 per cent; polymorphonuclear eosinophiles 1 per cent; lymphocytes 6 per cent; monocytes 13 per cent; myelocytes 8 per cent. On numerous occasions from 1 to 4 normoblasts per 100 white blood cells were seen. The reticulocytes were 2.6 per cent. There were moderate poikilocytosis, anisocytosis, polychromatophilia and basophilic stippling of the red blood cells. The mean corpuscular volume was 66 cubic microns, the mean corpuscular hemoglobin was 22 micro-micrograms and the mean corpuscular hemoglobin concentration was 35 per cent.

Roentgenograms of the pelvis showed that the sacrum and both innominate bones had increased in density and contained areas of coarse trabeculation. In both femora were areas of decalcification and increased density producing an appearance of coarse trabeculation in the medullary canals. Similar areas were seen in the humeri. Conclusions: von Recklinghausen's neurofibromatosis of the bone marrow.

Biopsy of sternal marrow: The bone marrow was replaced almost entirely by tumor tissue. The cellular arrangement was moderately dense and the blood vessels contained in it stood out prominently on rounded structures surrounded by tumor tissue. The cells of the tumor tissue were markedly pleomorphic and hyperchromatic. Many of the cells were long, slender, undulating and arranged in wavy bundles, often with a fascicular or whorled appearance. Large dark multinuclear giant cells and mitotic figures were frequently seen. Diagnosis: neurofibroma of the sternum.

Multiple Myeloma (Plasmacytoma)

Case 5. J. P. S., a white American male, aged 53 years, entered the University of California Hospital on March 8, 1937, because of pain in his chest and epigastrium, weakness and loss of weight. His illness started three months prior to entry when he noticed weakness, generalized aches and malaise. Soon thereafter he became aware of pain high in the epigastrium and over the anterior and lateral parts of the chest. He described the pain as being sharp and sufficiently excruciating to inhibit cough and deep breathing. During the course of illness the pains became so generalized that

movement of any part of the body caused discomfort. Since the onset of illness he had been confined to his bed almost constantly because of weakness and pain.

Physical Examination. The patient appeared weak and cachectic. The skin and the mucous membranes were pale. The lymph nodes were not enlarged. The head was of normal contour and no tenderness was elicited on pressure. Many points of tenderness were noted over the ribs anteriorly, in the axillae, and over the sternum. No abnormalities were found in the heart or lungs. Neither the spleen nor the liver was enlarged. Pressure on the pelvic bones caused excruciating pain.

Laboratory Data. The blood count showed: hemoglobin 44 per cent (6.4 gm.) Sahli; erythrocytes 1,790,000 per cubic millimeter; leukocytes 5,200 per cubic millimeter. The differential count showed: segmented polymorphonuclear leukocytes 20 per cent; non-segmented leukocytes 23 per cent; eosinophiles 3 per cent; basophiles 3 per cent; lymphocytes 20 per cent; monocytes 5 per cent; myelocytes 9 per cent; plasma cells 17 per cent. The normoblasts varied from 1 to 7 per 100 white blood cells. Anisocytosis and poikilocytosis of the red blood cells were marked. The platelets were 200,000 per cubic millimeter. The blood uric acid was 4.6 mg. per 100 c.c. The Wassermann and Kahn tests for syphilis were reported negative. The blood serum protein showed: total 9.21 per cent; of this 2.5 per cent was albumin and 6.71 per cent was globulin; the ratio of albumin to globulin was 0.37. No Bence-Jones protein was found in the urine. Roentgenograms showed that the clavicles, scapulae, ribs, lumbar vertebrae, pelvic bones and upper parts of the femura contained innumerable "punched out" areas. The trabecular structure of the bones was altered so that striations were not visible and there was very little evidence of calcium. Conclusion: multiple myeloma.

Biopsy of sternum: Sections of sternal marrow removed for biopsy showed almost complete replacement of the cells normally present by a large mononuclear type of cell. The membrane of the cells was distinct. The cytoplasm was brightly eosinophilic and finely granular. The nucleus was large and occupied almost all of the cell; it was basic and contained coarsely divided chromatin material which was distributed largely about the periphery. Many of the nuclei contained nucleoli. Diagnosis: plasmacytoma.

Clinical Picture

In many of the patients the symptomatology was poorly defined. The symptoms presented were variable but perhaps the most frequent was weakness. The onset was usually insidious. During the course of the illness some of the patients became distressed by palpitation and dyspnea. Evidences of hemorrhagic diathesis in the form of a generalized purpura or a petechial eruption was observed in three of the patients.

The physical examinations yielded a few striking findings. Most of the patients were poorly nourished and some appeared cachectic. The superficial lymph nodes were not enlarged. The spleen was enlarged in eight of the patients. In the patient with Gaucher's disease the spleen was of tremendous size.

Roentgen examination of the bony skeleton yielded interesting information. Abnormal findings were present in eight cases examined. Increased areas of density in the medullary cavities, osteolytic processes, rarefaction, alterations of the trabecular structure and a mottled appearance of the bones were some of the changes which suggested the presence of space consuming lesions in the bone marrow.

Case	Diagnosis	Hemoglobin		Red Blood Cells Millions per Cu. Mm.	Platelets per Cu. Mm.	White Blood Cells per Cu. Mm.	Polymorphonuclear Leukocytes %		Basophiles, %	Eosinophiles, %	Lymphocytes, %	Monocytes, %	Myelocytes, %	Plasma Cells, %	Nucleated Erythrocytes per 100 Leukocytes	Mean Corpuscular Volume	Mean Corpuscular Hemoglobin Concentration %
		%	Gm				Segmented	Non-segmented									
1*	Osteosclerosis	44	61	2.26	205,000	14,100	61	19			15	3	2			97	21
2†	Myelosclerosis	43	6	2.08	10,000	4,200	20	18			15	4	43		3		
3†	Myelosclerosis	85	11.9	4.95	300,000	68,500	16	51	1	1	8	1	19		2		
4*	Gaucher's disease	58	8.1	3.64	90,000	1,300	38	23	1		23	10	4		1	79	29
5*	Carcinomatosis from breast	23	3.3	1.22	25,000	5,400	30	20		2	20	1	19		30	101	32
6	Carcinomatosis from breast	58	8.4	2.83	200,000	6,030	20	18	1	3	37	5	16		22		
7	Carcinomatosis from stomach	41	5.7	2.40	50,000	8,250	27	30		3	29		11		7		
8*	Neurofibromatosis	60	8.2	2.78	180,000	3,450	51	21		1	6	13	8		4	76	35
9*	Multiple myeloma	44	6.4	1.79	200,000	5,200	20	23	3	3	20	5	9	17	7		
10	Multiple myeloma	43	6.0	1.75	43,000	2,700	21	24	1	10	38	1	5		1		

* Case history reported in text.
† See reference no. 4.

Blood Picture

From the accompanying table it will be seen that at the time of examination anemia of variable degrees was present in 10 patients. The content of the blood was not altered by recent transfusions or treatment. The erythrocytes varied in number from a high level of 4,950,000 cells to as low as 1,200,000 cells per cubic millimeter. The anemia could be considered severe in one patient, of moderate degree in eight patients and of slight degree in one patient. The level of the hemoglobin was reduced in proportion to or slightly in excess of the erythrocytes, so that the color index ranged between 0.7 and 1.2. There was marked variation in the size and shape of the erythrocytes, and polychromatophilia or punctate basophilia were in evidence in all of the blood films. Nucleated red blood cells were noted in the stained films of nine of the patients; they varied from 1 to as high as 30 per 100 leukocytes.

Specimens of blood for the estimation of the volume of packed cells were obtained from five of the patients. It is to be noted in the accompanying table that the mean corpuscular volume was within normal range. The mean corpuscular concentration of hemoglobin showed normal or slightly reduced values. Accordingly the anemia could be classified as normocytic and normochromic.

In the cases reported here it is to be noted that with one exception neither the quantitative nor the qualitative changes typical of true leukemia were present in the leukocytic formula. The white cell count was reduced below 5000 cells per cubic millimeter in five of the patients, was within normal range in three and was greatly increased in two. A shift to the left in the granulocytes was shown by an increase in the non-segmented polymorpho-

nuclear leukocytes. Myelocytes comprised from 2 to 43 per cent of the total cells, which in the presence of leukopenia indicates an absolute increase of considerable degree. Careful examination of the blood films failed to show the presence of myeloblasts.

The blood platelets were reduced in six of the patients. In three of the patients there was a distinct thrombopenia accompanied by purpuric manifestations, namely, spontaneous bleeding from mucous membranes, petechial hemorrhages into the skin, prolongation of the time required for a clot to form, and the subsequent formation of a soft non-retractile gel.

Structural Changes of the Bone Marrow

The photomicrographs shown in figures 1 to 5 correspond to case histories 1 to 5 respectively. Histologically the changes in the marrow were marked but varied in character depending upon the type of process involved. In each of the sections studied the normal orderly arrangement of the hematopoietic cells in the interstices of the fat was disturbed. The outstanding structural changes were: sclerosis of the marrow cavity by an ingrowth of connective tissue, displacement of marrow by conglomerations of tumor cells, and pressure atrophy of the tissue normally present by invasive or infiltrative lesions.

Fig. 1. Bone marrow showing osteosclerotic changes and hypoplasia of erythropoiesis and myelopoiesis.

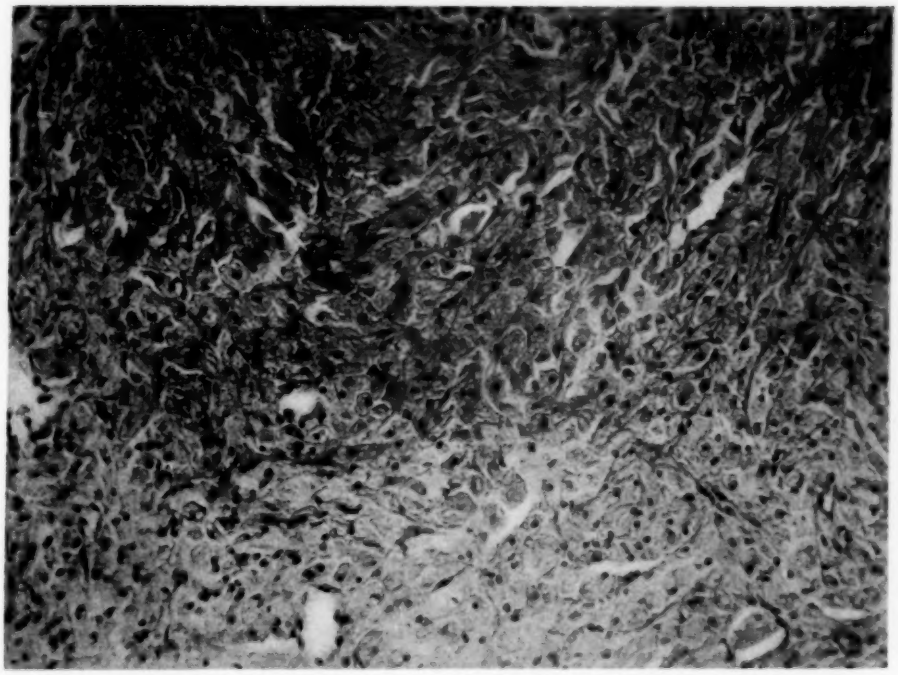

FIG. 2. Gaucher's disease showing kerasin containing cells in the bone marrow.

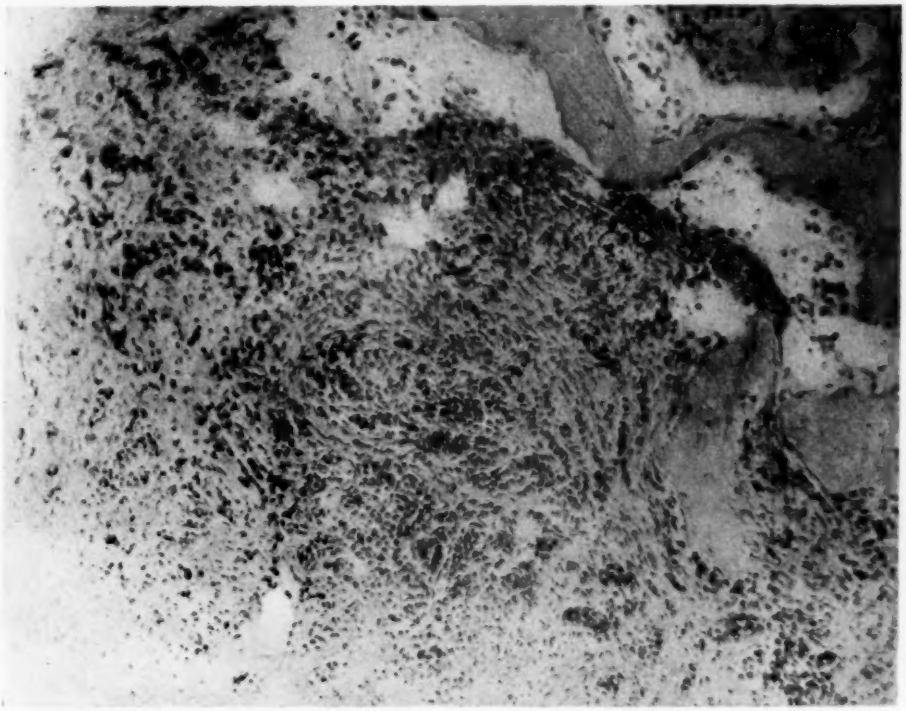

FIG. 3. Sternal bone marrow replaced by carcinomatous metastases from breast.

FIG. 4. Von Recklinghausen's disease; showing bone marrow replaced by neurofibromatous tissue.

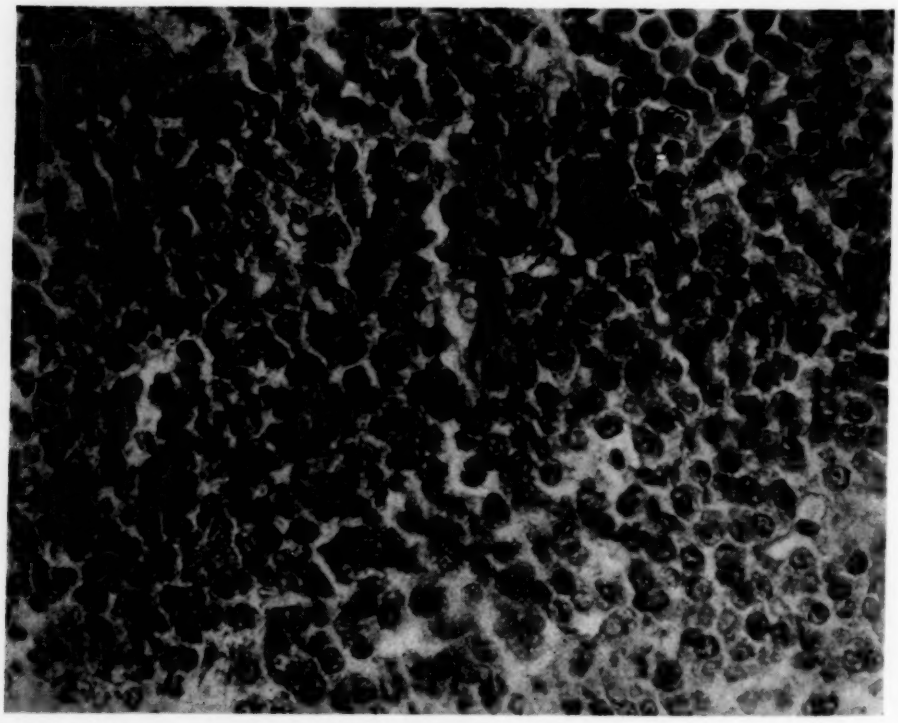

FIG. 5. Plasma cell replacement of bone marrow. Note almost complete absence of erythropoiesis.

The obviously active hematopoietic tissue was greatly reduced. Isolated groups of erythropoietic or myelopoietic cells could be seen between strands of connective tissue or among the tumor cells. Although the pathologic process varied in the different cases, the findings of a few myeloblasts, comparatively large numbers of myelocytes and a few segmented cells seemed to be common to all. Normoblasts and a few erythroblasts represented erythropoiesis. The replacement of the marrow by the sclerosing or infiltrating processes and the altered anatomic arrangement of the marrow cells, it is believed, could account for the hematologic picture of anemia, normoblastosis, leukopenia and a shift to the left in the leukocytic formula.

Discussion

In the 10 patients whose hematologic data are presented here space consuming lesions of the bone marrow were found. Following biopsy of the sternum the diagnoses were: myelosclerosis in two patients, osteosclerosis in one patient, neurofibromatosis in one patient, Gaucher's disease in one patient, carcinomatosis in three patients, and multiple myeloma in two patients. The anemia was characterized by moderate severity and was of a normocytic-normochromic type. Since the abnormal tissue caused mechanical alteration of the marrow, the anemia could be designated in the etiological classification as myelophthisic or simply as disease of the blood formative tissue due to marrow replacement. Normoblastosis and myelocytosis were observed in all the stained films of blood. The cases were reported because of their rarity and because of the difficulties encountered in making a differential diagnosis from aplastic anemia or aleukemic myelosis.

Aplastic anemia can usually be differentiated from myelophthisic anemia by the lack of signs of regeneration of the red blood cells in the former. Rhoades [7] recently promulgated the idea that some cases of sclerosis of the bone marrow should be classified as sub-groups of aplastic anemia. The basic defect he believed could be attributed to an arrest of maturation of erythropoiesis as a result of replacement of hematopoietic cells and associated with an absence of immature cells in the blood.

In the cases reported the resemblance of the hematologic findings to aleukemic myelosis is striking. In a recent study of this disease [8, 9] it was observed that normoblastosis was a constant finding. The anemia was normocytic and normochromic. A difference noted in the differential formula, however, was a shift to the left to include not only myelocytes but also myeloblasts. This close similarity of the anemia in this group to that in patients with sclerosis of the marrow suggests that abnormal erythropoiesis may be an arrest of maturation induced by the deranged anatomical structure of the marrow.

It must be emphasized that the diagnosis of the unusual type of anemia presented here may be suggested by the myelocytic-normoblastic reaction, substantiated by the roentgen films of the bones and usually confirmed by

biopsy of the sternum. Specimens of marrow removed from the marrow cavity with a curette will show an altered architecture when properly fixed and sectioned. An attempt to remove representative tissue from the medullary cavity by the "puncture" method may prove disappointing. Hematopoietic cells may be obtained but the more compact neoplastic and sclerotic tissues will be retained by virtue of their desmoplastic reaction.

Conclusions

A description is given of the hematologic aspects of space consuming lesions of the bone marrow. The group comprised 10 patients among whom were cases of myelosclerosis, osteosclerosis, neurofibromatosis, Gaucher's disease, carcinomatosis and multiple myeloma. The clinical findings were a moderately severe anemia, leukopenia, seldom an increased white count, and the presence of myelocytes and normoblasts in the stained films of blood.

The anemia is normochromic and normocytic. Myelophthisic anemia or disease of the blood formative tissue due to marrow replacement may be used as descriptive terms in the etiologic classification.

The similarity of the anemia in aleukemic myelosis to this type of anemia is discussed.

The value of examining the bone marrow by biopsy of the sternum in preference to the puncture method is emphasized.

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ERYTHEMA MULTIFORME EXSUDATIVUM (HEBRA); A CLINICAL ENTITY ASSOCIATED WITH SYSTEMIC FEATURES *

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CUTANEOUS lesions labeled as erythema multiforme are often encountered in medical practice. Variations in clinical course, a complicated nomenclature, and the artificial hiatus separating dermatology from internal medicine have been contributory factors in making a difficult subject even more involved. The literature is replete with controversies regarding the conception of erythema multiforme and the so-called erythema group of skin diseases. Though from time to time well-defined entities have been differentiated from this all-inclusive category, the concept of erythema multiforme, as described in the average American textbook on dermatology, still comprises a multitude of heterogeneous eruptions. It is true that the skin may react to the same morbid agent in a variety of ways (Besnier's dictum), and it is also certain that there are abundant transitions between well-characterized conditions (Brocq's réactions cutanées), creating difficulties in the differential diagnosis. Yet, study of dermatoses in terms of the internal medical manifestations will often reveal features or combinations of features that permit accurate classification.[1] This principle has hardly received the consideration it deserves.

The diagnosis of erythema multiforme or multiform erythema (toxic erythema) may be regarded as purely descriptive. In truth, it affords no clear insight into the nature of the general underlying process, and, what is also important, it adds little information about classification and still less about prognosis. Already there are manifest signs of a trend that decries the descriptive method, but this view is based on the supposition that morphology has reached its peak and exhausted its possibilities. This belief is, however, only a half-truth, and nothing illustrates the point better than a study of the eruptions comprised within the category of erythema multiforme. The time appears to be ripe to attempt a subdivision of this *caput mortuum* into a number of entities. In the average case these conditions may be separated from one another with comparative facility, if studied in terms of the composite clinical picture and in the light of instances seen not only in private practice and dispensaries, but also in the medical wards. These differentiations are essential to the proper grouping of cases for further investigation; moreover, methods of treatment may be employed rationally and a more accurate prognosis formulated. However, there may be difficulties in diagnosis owing to the occurrence of what seem to be transitional instances, and these cases should be placed to one side for subsequent study.

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In several previous papers I have discussed the features of "erythema multiforme" as observed in gonococcal bacteremia,[2] rheumatic fever,[3] and systemic lupus erythematosus.[4] In this communication it is my intention to describe the cutaneous and internal medical manifestations of what is probably a specific clinical entity—erythema multiforme exsudativum (Hebra). The data collected for this article are based chiefly on the personal observation of many isolated instances and several endemics of the disease. It may be put down as an axiom that when one example of this condition is seen many others are likely to be encountered at the same time.

Historical Data

Dermatologic analysis of the erythemas may be said to have begun with the work of Willan (1808)[5] and his pupil Bateman (1814).[6] Fundamental observations in morphology were contributed by Rayer (1835)[7] and Bazin (1862).[8] From the many varieties of eruptions classified in this category Hebra (1860)[9] differentiated a specific entity to which he gave the name erythema exsudativum multiforme. The importance of his endeavors lay primarily in the assembling of apparently diverse cutaneous lesions under one head and the recognition of the principle that they represented phases of a single condition. However, Hebra stressed morphology alone, and regarded the affection as essentially benign. Although Bazin[8] denied the unity of the several variants, he was the first to recognize the occurrence of lesions in the mouth and the prodromal constitutional symptoms in the vesiculo-bullous type of erythema multiforme exsudativum (hydroa vésiculeux); moreover, he clearly distinguished the herpes iris originally described by Bateman from the herpes circinatus (ringworm) attributable to fungus infection. Quinquaud (1882)[10] added an admirable account of the oral manifestations, while Kaposi,[11] Besnier and Doyen[12] and others emphasized the systemic features. In 1884 Leloir[13] furnished a masterly exposition of the pathologic anatomy of these eruptions. In the same year Duhring[14] segregated the clinical syndrome dermatitis herpetiformis. Even a part of pemphigus had to be salvaged from the inclusive category of erythema multiforme. Since then numerous dermatologists[11, 15, 16, 17, 18] and internists[19, 20, 21, 22] have concerned themselves with various phases of the subject, the opinions expressed being most diverse. In many cases futile debates arose because each observer was familiar only with his own special field. It is interesting, for example, to contrast the conception of the erythema group of skin diseases proposed by dermatologists[23] with that generally held by internists (Osler's erythema group).[22, 24] Throughout the history of these affections and even to the present time, the field has been dominated and obscured by vague notions regarding "arthritism," "rheumatism" and rheumatic fever. The major difficulty appeared to arise from certain resemblances in the clinical features presented by the various conditions. For example, there are at least six types of so-called erythema multiforme manifesting cutaneous lesions, joint pains, cardiac murmurs of functional or

organic origin, fever, and even prodromal sore throat; yet study of the composite clinical picture and of the attributes shown by the eruptions reveals significant differences in a high percentage of cases. It is possible to recognize the nature of the "erythema multiforme" in most of the instances recorded in the older literature, though the titles under which they were described were often vague and sometimes erroneous.

In its principal outlines the conception of this disease as an entity seems to be accepted by many European dermatologists.[25, 26, 27] Indeed, this is the only type regarded as meriting the title erythema multiforme or erythème polymorphe, all other simulating eruptions being classified in the category of "symptomatic polymorphous erythemas" or "toxic erythema." For the most part American dermatologists[16] tend to deny the authenticity of Hebra's erythema multiforme exsudativum, a notable exception being Klauder.[28] My own observations appear to support the belief that this disease is a specific entity; that, at least in New York City and its environs, it is not rare during the spring and autumn months; but that it is usually labeled with a variety of names, of which the most common is "toxic erythema."

Definitions

In its broadest sense the term erythema multiforme is used to designate erythemato-papular rashes of relatively acute onset and brief course, showing special favor for the extensor aspects of the limbs; this holds especially in the case of eruptions that cannot be classified precisely.* In many instances there may be added a vesicular, pustular or bullous component, but these elements are facultative. Realizing that this descriptive basis for classification has shortcomings, some have employed the name "multiform erythema" in a comprehensive sense similar to that enjoyed by the generic term polymorphous erythemas. Recent reports in the French literature[26] indicate that an attempt is being made to restrict the designation erythème polymorphe to the specific entity described by Hebra. It is probable that the term "multiform erythema," often used expediently, will be applied less frequently as specific conditions are segregated from this heterogeneous group.

The qualifying word "multiform" requires explanation. It was probably first introduced by Hebra for the purpose of indicating the close relation existing between several dermatologic lesions that had been previously classified in separate categories; for example, erythema papulatum, erythema marginatum, erythema tuberculatum, herpes iris, etc., etc. It was, however, soon recognized that at any given moment the lesions might be of a single type; under such circumstances the eruption hardly merited its full descriptive title. On the other hand, continued observation in many such cases revealed polymorphism arising from (1) variations in the development of individual lesions, and (2) the introduction of new types of efflorescences,

* For example, Kaposi included lichen urticatus which is now recognized as a separate entity, allied to urticaria (papular urticaria).

either in fresh crops or in subsequent recurrences of the condition. So far as polymorphous eruptions were concerned it was also noted that other diseases, such as dermatitis herpetiformis and acute lupus erythematosus, were often accompanied by lesions that were just as multiform in appearance as those in erythema multiforme exsudativum. It will be seen, then, that polymorphism cannot be used as an absolute criterion in the classification of disease. Despite this, the term erythema multiforme seems destined to be retained in nomenclature, its meaning being variously restricted or broadened.

Clinical Data

The cutaneous manifestations observed in erythema multiforme exsudativum may be conveniently classified in two groups, with numerous transitions: (1) erythemato-papular type; (2) vesiculo-bullous type. Both variants may be encountered in the same patient, either simultaneously or in subsequent crops or in later recurrences of the affection. The most striking features are: (*a*) the morphologic attributes of the cutaneous lesions; (*b*) definite predilection for certain parts of the body; (*c*) constitutional symptoms in a high percentage of cases; (*d*) a seasonal incidence in many instances and occurrence in endemics; when many cases are observed the impression of an epidemic may be created; (*e*) recurrences, especially during autumn and spring; (*f*) predominant incidence in young adults, though no age seems to be entirely spared.

The affection generally runs its course in from two to three weeks, but it may be prolonged one or two months, occasionally even longer. It is not uncommon to observe pigmented spots, the sequelae of healed lesions, for many months. Persistence of the disease is usually caused by the appearance of fresh crops of efflorescences, recurrent attacks of the systemic complaints, or the supervention of a complication, such as bronchopneumonia. The eruption is generally not chronic in the sense that individual lesions require a long time for involution. When, as in the rare examples of conjunctival and corneal involvement, residual changes remain visible or progressive in type, this is probably due to the nature of the affected structures and its potentialities for secondary infection, not to chronicity in the affection itself.

Cutaneous Lesions

1. Erythemato-Papular Type. The papular variety exhibits striking favor for the dorsa of the hands, this site being first affected, though by no means invariably. The eruption then extends symmetrically in one or more crops along the extensor aspects of the forearms, sides of the neck, lateral aspects of the face, and on the forehead. This manner of spread is of diagnostic import, especially when the lesions on the hands are not typical or when they are first seen in the process of involution. The dorsa of the feet and the extensor surfaces of the legs and knees are often involved, the lesions spreading upwards in crops, as in the case of the upper limbs. The palms,

soles, arms, thighs, inner aspects of the perineum, back of the neck near the scalp line, and the trunk are other areas occasionally affected, but no portion of the body is spared, with the possible exception of the scalp proper. Even the latter part of this rule may have exceptions, though I have not met with them. The incidence with which the various areas are involved differs with individual accounts, but this is of no great moment, as the eruption exhibits a characteristic pattern in most cases. The average duration of each crop is from six to 10 days, but lesions situated on the face and lobes of the ears appear to undergo more rapid involution, roughly in from three to five days in the instances under my observation.

The primary element is an erythematous macule that speedily becomes elevated (papule), owing to the increased intensity in the exudative phenomena (edema and perivascular infiltration). When there is pronounced exudation of fluid the elevation shows attributes resembling ordinary urticaria (urticarial component). The center of the papule generally acquires a characteristic peculiar violaceous hue, attributable to tremendous congestion and stagnation of blood in the vessels occupying the upper and middle portions of the cutis. As the lesion spreads peripherally the central portion becomes relatively depressed and cyanosed, whereas the advancing border is raised above the level of the skin in a bright red fringe. In occasional instances, as in two cases under my observation, this characteristic evolution was abortive, and the papules showed a peculiar brownish red hue; under such circumstances recognition of the eruption becomes more difficult and the diagnosis must perforce be based on the manner of spread and the general features of the affection.

In other cases there is centrifugal extension of the borders. Coalescence of contiguous lesions results in the formation of marginated figures of various sizes, shapes and complexities, the enclosed areas being discolored. In its morphologic attributes this variant resembles erythema marginatum rheumaticum, the differential features of which will be summarized in another section of the article.

Thus far I have described the simple papular efflorescence and its manner of evolution. A more characteristic appearance illustrating the essential nature of the process is that furnished by the so-called erythema iris and its variants. This name has been applied to various lesions, but the fundamental principle is that within a short time, generally measured in days, there occurs resumption of activity in the centers of efflorescences, with or without subsequent peripheral spread of the recent focus. Thus, the centers may show a fresh bright-red papule, vesicle or bulla, or there may be concentric rings of various hues, creating an iridescent pattern owing to the differences in the stages of evolution from center to periphery. This process may repeat itself several times, with the production of complicated iris figures showing an astonishing play of colors; in principle, however, these lesions merely represent examples of erythema papulatum characterized by central relapses, with or without evidence of subsequent centrifugal spread.

Involvement of the mucous membranes and the occurrence of constitutional symptoms may accompany the papular type of erythema multiforme exsudativum. However, these manifestations are usually seen less often and are generally less pronounced than in the case of the vesiculo-bullous variety and may, indeed, be altogether wanting. This rule, however, admits of many exceptions. One of the most important of these concerns the cases characterized by profuse papular lesions found on the trunk; apparently this type is accompanied by systemic reactions in a large proportion of instances, and its occurrence may be regarded as evidence of increased severity in the disease. The few cases grouped under the title of Stevens-Johnson syndrome [29] appear to fall in this category. The lesions in the mucous membranes and the constitutional symptoms will be discussed in greater detail in later sections of this article.

2. Vesiculo-Bullous Type. This variety is often seen by internists, pediatricians and ophthalmologists. Numerous examples have been recorded under diverse titles and a prolific patronymic nomenclature has arisen. Of historical interest was the polemic between Gerhardt [20] and Kaposi [11] relative to the classification of this disease, the controversy having concerned the status of cases originally recorded by Wunderlich [19] as "phlyctenular fever." The more recent literature also contains opinions reflecting significant differences in conception.[29, 30, 31, 32, 33, 34] The group of cases reported by Meyer,[35] for example, under the title of "acute articular rheumatism with erythema pustulosum" were probable instances of vesiculo-bullous erythema multiforme exsudativum accompanied by secondary clouding of vesicles, rather than examples of genuine rheumatic fever. It may be stated, parenthetically, that the cutaneous lesions in rheumatic fever rarely, if ever, show a vesicular, bullous or pustular component, and that in the excessively uncommon instances where such phenomena have been described the diagnosis was doubtful.[3]

In general, the eruptions considered in this section are the counterpart of papular erythema multiforme exsudativum, except that exudation of fluid and cells is so intense as to result in the formation of vesicles and bullae, usually centrally disposed. It is common to observe a vesicle or small bulla capping the centers of papular lesions. The name herpes iris is generally applied either to those efflorescences revealing the appearance just described or to configurations of vesicles or bullae arranged concentrically. As in the case of erythema iris, these lesions or variants of them arise from repeated local central recurrences, with or without peripheral spread of each fresh focus and, similarly, there may be a play of colors from the center to the periphery. The occurrence of pustules is attributable either to clouding of vesicles or superimposed infection and, as such, represents a secondary rather than a primary element in the eruption.

Features of Special Interest

Before describing the less characteristic lesions in the mucous membranes it appears desirable to analyze a number of special features. The recog-

nition of these points is essential in understanding the protein disease erythema multiforme exsudativum.

1. Age and Sex. Though the affection is encountered most commonly in young adults of both sexes, it may occur at any age, including the extremes. Schlesinger [36] observed that the disease may be more severe in the average example of erythema multiforme exsudativum seen in children, but this rule, though valuable, is not without exceptions.

2. Subjective Symptoms. As a rule the eruption runs its course, without the occurrence of striking subjective complaints, aside from a trifling sense of burning in some cases; at times there may be a degree of pruritus, but this is rarely intense. This rule is, however, violated in many patients presenting lesions in the mucous membranes, as will be noted later.

3. Influence of Location. The morphologic attributes may be considerably modified or influenced by location. Thus, lesions in the soles and palms tend to remain macular, owing to the unyielding thick epidermis in these situations. Efflorescences appearing on the lower limbs may become nodular, somewhat painful, and assume a bluish hue, with decided resemblances to erythema nodosum [12, 27, 37, 38, 40]; these modifications are often exhibited by many dermatoses affecting the lower extremities,[39] and they are correlated best with the nature of the involved tissue (poor circulation) and the probable occurrence of pathologic alterations in the deeper parts of the cutis and the adjacent areas. Lesions situated in the mucous membranes are modified profoundly for reasons that will be noted in another section of the article.

Edematous infiltrations are occasionally encountered in various parts of the body, and they may arise from a variety of causes: (*a*) the tissue may be of loose texture (eyelids, prepuce, labia majora, lips, etc.); (*b*) the exudation of edematous fluid may be especially intense or may be favored by anatomical relations (dependent parts, etc.); for example, there may be localized swellings in the face, tongue, hands and legs. I have seen on several occasions the dorsa of the hands so markedly swollen as to interfere with closing of the fists. This attribute, though usually of brief duration, is not to be confused with angioneurotic edema or true urticaria.

4. Scaling, Crusting and Desquamation. The simple papular efflorescences in erythema multiforme exsudativum may be attended occasionally by slight scaling, but these scales appear not to show the adherent qualities or the "carpet-tack" appearance seen in lupus erythematosus. In some cases this phenomenon may be attributed to the presence of vesicles that are generally visible, sometimes inconspicuous and ephemeral. Crusts may be formed consecutive to the rupture of vesicles or bullae, but it is also possible for these to resorb completely, without leaving any sequelae. The occurrence of rapid absorption or drying of lesions produces the appearance of scales, rather than crusts; under such circumstances a widespread bullous eruption may be succeeded by what is popularly interpreted as ordinary desquamation. In a case recently observed by me, through the kindness of

Dr. Harry A. Solomon, the hands, which had been the site of closely apposed bullae, revealed as an aftermath the appearance of large epidermal lamellae, with exposure of the underlying bright-red smooth epidermis. Phenomena of a similar order have been encountered by other observers.[41, 42, 43]

It will be seen, then, that the occurrence of desquamation of this type, in the presence or apparent absence of obvious exudative lesions, affords no basis for the belief that the clinical picture is distinct from erythema multiforme exsudativum.

5. Pigmentation and Depigmentation. Areas colored various shades of brown are often left in the wake of this eruption, and these may remain visible for weeks, occasionally for many months.[44, 45] It is to be emphasized that this occurrence is noted as a sequela, rather than as an accompaniment of the early stages in the lesions. It seems likely that the phenomenon is due, at least in part, to a degree of microscopic hemorrhage.[13, 12] There are, however, many instances in which pigmentation remains visible for so long a time as to awaken the belief that this is not entirely dependent on microscopic extravasations of blood; it appears probable that in such cases there is a secondary " inflammatory melanosis " similar to that encountered in drug eruptions, for example, those due to phenolphthalein.[47, 48] This I was able to substantiate in at least one patient from whom biopsy specimens were taken in the stage of involution, but it is a matter easily resolved by more extensive minute anatomical studies. The brown spots may be so widely distributed as to create a speckled appearance, but they are not accompanied by any degree of atrophy.

Rarely the lesions may fade, with the production of depigmented areas at the sites (leucoderma); this unusual sequela occurs variably even in the same patient, for it may be present in one attack, absent in others.[50]

6. Atrophy, Ulceration and Scarring. Atrophy secondary to pathologic alterations in the cutis is not observed in this affection, nor have I met with thinning of the epidermis in authentic examples of the disease. This interesting point merits notice, for in the superficial types of " systemic " lupus erythematosus the edematous fluid appears to possess different properties, resulting in atrophy or at least marked thinning of the epidermis.[4]

For various reasons to be mentioned later lesions in the mucous membranes often assume the form of erosions, but it is common to observe complete healing, and the production of cicatrices is rare; this affords evidence that the pathologic process is essentially superficial. My own observations are in agreement with those who deny the occurrence of ulceration as a fundamental method of healing in erythema multiforme exsudativum.[49] When ulceration occurs, especially in the mucous membranes, it represents probably the effect of secondary infection or of drastic treatment; this complication is seen more commonly in the mucous membranes, rarely in the skin, and is followed by scarring incident to granulation tissue.

7. Hemorrhagic and Aberrant Bullae. That bullae occur in erythema multiforme exsudativum is well established. It has also been observed, as in

several cases seen by me, that isolated lesions of this sort may occasionally appear without the usual erythematous halo.[12, 13, 44] This may result in decided resemblances to pemphigus, but, as stressed by Besnier, the diagnosis must be based on the totality of the eruption, rather than on a few isolated efflorescences.

Opinions differ, also, relative to the appearance of gross hemorrhage within bullae. Thus, Tachau,[27] who accepted the occurrence of microscopic extravasations of blood, denied the authenticity of cases of erythema multiforme exsudativum showing this phenomenon clinically. It seems true that many such recorded instances were lacking in essential particulars or were described under erroneous titles (examples of gonococcal erythema multiforme,[2] Osler's erythema group,[1] systemic lupus erythematosus, drug eruptions, etc.). Despite this, my own observations appear to support the belief that hemorrhagic bullae may occur occasionally, and similar findings have been noted by others in authentic cases of this disease.[37, 44, 52, 53, 54, 55] Two general features exhibited by this group of cases have caused hesitation in accepting this phenomenon as part of the affection: (1) the widespread distribution of the lesions, rendering difficult the recognition of the ordinary attributes of erythema multiforme exsudativum, especially in cases seen early in the course; (2) the common association with instances featured by severe constitutional symptoms. Intimately involved in this polemic is the status of the so-called Stevens-Johnson disease,[29, 84] which will be discussed in the section on the conjunctival and corneal changes seen in Hebra's erythema multiforme exsudativum.

8. Miscellaneous Atypical Features. In studying this disease there have come under my observation cases that were more difficult to recognize on account of the following features: (*a*) the eruption was restricted to a single or two crops in all, and the lesions were sparsely distributed; (*b*) the dorsa of the hands, a favorite site, were entirely spared or were affected relatively late in the course; (*c*) the eruption, rarely, showed a tendency to affect the flexor surfaces; when restricted to these areas, the condition has been called the "inverse" type, but similar atypical features may be exhibited by many other cutaneous affections; (*d*) occasionally lesions appeared on the "flush area" of the face and these by coalescence formed a more or less diffuse erythema simulating superficial lupus erythematosus, but these patches were characteristically transient; (*e*) the lobes of the ears were affected occasionally, a feature observed more commonly by Leipner[51] who met with it in 12 out of 30 cases; however, unless the eruption is transient, the possibility of lupus erythematosus or other dermatoses should be borne in mind. In the early stages the differentiation may be difficult, and I have seen a number of examples of lupus erythematosus in which the incipient lesions were diagnosed as erythema multiforme exsudativum, though the eruption did not present the typical features of the latter dermatosis. In one case, for example, the condition was regarded as hemorrhagic bullous erythema multiforme, with conspicuous involvement of the ears; after several years of

observation it became certain that this patient did not suffer from erythema multiforme exsudativum, though the precise nature of the malady was still obscure.

9. Relapses and Recurrences. Relapses in this affection are common. It is probable that exceptional instances featured by a prolonged course,[12, 56] measured in months or years, may be explained on the basis of this factor, though in some cases the distinction between a relapse and a recurrence was not always easy to determine. Aside from complications and sequelae the individual efflorescences in erythema multiforme exsudativum evolve in a relatively short time, contrasting, for example, with the chronicity displayed by the average lesion in pemphigus.

If cases of this disease are observed over many years and careful histories taken, it will be found undoubtedly that recurrences are relatively common. This feature is more often exhibited by the vesiculo-bullous form, but I have also met with it in several cases showing erythemato-papular rashes. Jordan [57] has roughly estimated the incidence of recurrences as 17 per cent, and the literature abounds with examples illustrating this fundamental point.[8, 9, 12, 45] Accurate statistics are, however, not available as yet. In addition, Hebra described an annual recurrent type, and it is not rare to observe repeated attacks at certain seasons, especially autumn and spring,[12, 58, 45] though there is often great variability in this respect.

In many instances the same type of eruption recurs. I must, however, agree with those who have noted variations not only in regard to morphologic attributes, but also in regard to location of lesions.

10. Endemics and Epidemics. It has been stated that the observation of one case generally means that more patients of this sort will be seen shortly. This is explained, in large measure, by the factor of seasonal incidence (spring and autumn), though isolated instances may be encountered throughout the year. The occurrence of this disease in minor or major epidemic proportions has been recorded by many writers.[51, 55, 58, 59, 60, 61] In most instances these epidemics concerned soldiers who were quartered in the same barracks or nearby. It is, however, more common to encounter the affection in endemic form, especially at the favored seasons, as I have observed several times. The disease is occasionally met with in several members of a family, but on the whole this is an uncommon occurrence. In a few instances other patients in the same medical ward have been found to become affected by this condition. There is, however, no definite evidence that erythema multiforme exsudativum is a contagious disease, directly transmitted from one person to another.

11. Alliance Between the Papular and Vesiculo-Bullous Forms. Although Hebra discussed herpes iris and its variants under the general category of Herpes, he presented cogent reasons for allying these lesions with the papular form. To summarize: (*a*) both types may appear in the same person, either simultaneously or subsequently; (*b*) they show similar sites of predilection and their clinical course is fundamentally alike; (*c*) recur-

rences are observed in both types and these manifest the same seasonal incidence. The data recorded in the literature and in this paper appear to substantiate amply this fundamental relation.[27, 45, 58, 62, 63]

12. Coincidental and Concomitant Disease. The evaluation of the factor of coincidence in diseases and the possible influence of one affection upon another has always been a delicate problem. There is no evidence indicating that erythema multiforme exsudativum confers an immunity against any other condition. There is still less ground for denying the occasional close similarities in clinical picture between erythema multiforme exsudativum and a host of simulating diseases, as will be noted in discussing the differential diagnosis. There is, however, one affection requiring brief mention at this time, namely, "nephritis." This has been regarded by some as a frequent concomitant of erythema multiforme exsudativum, but, in agreement with the opinion expressed by Tachau, I am unable to substantiate this relation.

In analyzing closely the older reports, it appears that the following criticisms are justified: (*a*) the criteria for the diagnosis of "nephritis" were often inadequate; (*b*) no systematic effort was made to differentiate the various types of renal involvement, and but few reports contain adequate minute anatomical data; (*c*) there are many recorded instances showing disease in the kidneys, but, as stressed by Tachau, the diagnosis of the eruption was often erroneous; (*d*) the factor of coincidence was not taken into consideration. There are undoubtedly a few recorded cases exhibiting the combination of true inflammatory nephritis with renal failure and erythema multiforme exsudativum or an eruption simulating it. In 1932 Chargin and I [64] analyzed the data found in 1100 records of various types of renal disease in respect to the dermatoses encountered. Since then many additional rashes of this sort have come under my observation, and it appears that the problem is chiefly concerned with cutaneous lesions occurring in the period of renal insufficiency (uremides or nephritides). It can be said that eruptions resembling erythema multiforme are extremely rare, and the literature contains but few authentic instances illustrating this combination; nor is it always clear that both occurred in close temporal relation. There are cases in which it appears that the onset of renal disease antedated by many months or years the appearance of erythema multiforme exsudativum or a rash resembling it, the cutaneous lesions having been seen in the period of azotemia; on the other hand, it is possible that erythema multiforme exsudativum may have an unfavorable influence on previously damaged kidneys for reasons to be mentioned later. It would seem that the entire subject is in want of fresh clinico-pathologic investigations.

On one point, however, there appears to be some certainty. Eruptions encountered in uremia are apt to become hemorrhagic. This phenomenon I have observed many times; for example, tinea cruris (eczema marginatum) may acquire a secondary hemorrhagic component during the course of an intense azotemia; scratch marks with superimposed linear hemorrhages may be a revealing sign of renal insufficiency; drug eruptions may assume a

bluish hue due to extravasation of blood in excess of what is to be normally expected.[45] It has been claimed that necrosis of cutaneous lesions, analogous to that seen in the gastrointestinal tract, is often encountered, but my observations appear not to substantiate this belief, though the post-mortem examinations in many such instances revealed a fair incidence of superficial necrotic areas along the gastrointestinal tract. The one exception was a case of hemorrhagic gangrenous herpes zoster of the trunk occurring in a patient dying in uremia, but, as the former may reach a similar degree of intensity under ordinary circumstances, it was difficult to assess the importance of the phenomenon. However, it seems likely that hemorrhage of pronounced degree, as is often observed in the cutaneous lesions in uremia, may be accompanied secondarily by disintegration of tissue. In another section of this paper the relation between erythema multiforme exsudativum and nephritis will receive further consideration.

13. Isomorph Reizeffekt. Under the term Köbner's phenomenon dermatologists have long recognized that normal areas of skin in patients with psoriasis will often reproduce the primary lesions of that disease when subjected to various types of trauma. It was later found that a few other affections, of which lichen planus is a conspicuous example, may exhibit this behavior, and this property is sometimes utilized in the form of a test in obscure cases. Kreibich,[65] who has actively concerned himself with this "isomorph reizeffekt," observed it in several classical examples of vesiculobullous erythema multiforme exsudativum as well as in erythema nodosum; this phenomenon he was able to demonstrate with the use of such various agents as trichophytin, isotonic saline solution, sterile distilled water, scratching the skin or excoriating it with a needle. Kogoj[66] has apparently substantiated, in principle, the observations of Kreibich in erythema multiforme exsudativum, and has further shown that the results obtained by such traumas depend often on the time the experiment is conducted. This phenomenon is important in evaluating the significance of the agents that have been or will be used in an effort to trace the etiology of this and other affections, for example, the employment of streptococcal extracts, tuberculin, trichophytin, etc. In all cases it will be essential, by means of appropriate controls, to differentiate a specific reaction from the non-specific "isomorph reizeffekt."

Lesions in the Mucous Membranes

Involvement of the mucous membranes is an integral part of the disease erythema multiforme exsudativum. Its incidence has been variously estimated at from 25 per cent to approximately 60 per cent; the former figure appears to be more nearly accurate. It may be laid down as a general rule that, with but few exceptions, the dangers and the prognosis of this affection are proportionate to the severity of these manifestations. In the ordinary papular type the mucous membranes are generally spared, but there are many exceptions; it is essential, therefore, to examine these parts in every patient,

as isolated lesions may be present even though there are no subjective symptoms attributable to them. On the other hand, oral manifestations may be the only or the most striking feature in this disease, especially in the vesiculobullous form. It is not rare to encounter instances in which these parts are affected early in the course, with cutaneous lesions appearing later in that attack or in a subsequent recurrence.

Casual study of the efflorescences in the mucous membranes would seem to reveal attributes differing from those observed in the skin; yet these differences are not fundamental, but rather related to the modifying influence induced by anatomical relations. In addition, the factor of inaccessibility to direct and prolonged examinations often handicaps the observer. In the mucous membranes, notably of the mouth, variations in color and shade are less evident; scales and crusts are not as readily formed; atrophy and scarring are recognized with less facility. More important, vesicles and bullae are rarely found intact, for the structure of the mucous membrane is looser than is the case in the skin, permitting more active penetration by exudative products, and the layer corresponding to the horny portion of the epidermis lacks the cohesion required to allow an accumulation of fluid beneath it in restricted compartments. Moreover, such local modifying factors as moisture and warmth, the maceration of sputum, and the trauma of chewing, and movements of the tongue aid in distorting the clinical appearances. Many types of lesions, therefore, acquire the form of superficial erosions. In the eyes, also, the influence of moisture and blinking probably plays a part in changing the attributes of the efflorescences. Finally, secondary infection often occurs as a complicating factor capable of inducing profound alterations in the original aspects of these manifestations. Aside from a few typical appearances, it may be laid down as a good general rule that the diagnosis of oral lesions often rests on exclusion and on the observation of an eruption in the skin. Nevertheless, closer study may reveal better criteria for the recognition of a large proportion of the manifestations found in the mucous membranes.

A. Oral Mucous Membranes. The early dermatologic literature contains sporadic references to the oral lesions seen in erythema multiforme exsudativum (Bazin, Lipp, Charlouis, etc.). It was Quinquaud,[10] however, who furnished the first comprehensive description of these changes, and subsequent observations have been concerned merely with additional morphologic details. Quinquaud recognized an initial erythematous stage, the enanthem appearing as small red spots, round or oval in shape, and persisting in this form only a few hours. This is followed by the formation of vesicles and bullae. Owing to the local factors already enumerated, the efflorescences become superficially eroded, covered by a whitish membrane or fringed by fragments of torn epithelium, and circumscribed by an erythematous border. Finally, healing takes place, without the production of sequelae, though brownish macules marking former sites of enanthem may persist several weeks. Occasionally faint white scars may be observed,[54]

but it appears that cicatrization represents not an inherent method of cure, but rather the result of secondary infection and ulceration.

The favorite sites of the enanthem are the buccal mucosa, vermilion of the lips, and the hard and soft palates, but other areas may also be affected. In one case under my observation there occurred almost complete ulceration of the uvula, a probable sequel to secondary infection. The process extends occasionally to the pharynx, larynx, tracheobronchial tract and, rarely, to the esophagus; it is the involvement of these parts that accounts for a large proportion of the lethal complications, as will be described later.

Subjective symptoms may be absent or mild in many instances, but there are examples featured by especially severe complaints. A complete description of these manifestations will be deferred until the internal medical features of this affection are considered, for they merge imperceptibly.

The average appearance of lesions at the height of development, then, is that of a superficial erosion covered usually by a whitish membrane and surrounded by a peripheral dark red or violaceous red zone several millimeters wide. Sometimes the central deposits are yellowish or distinctly hemorrhagic. The overlying membrane is usually soft and pulpy in consistency, and, when wiped away with a cotton plug, leaves bleeding areas. Other variations in appearance seem to be determined in large part by the location of the enanthem. There are instances in which only a diffuse redness of the mucous membranes is found; on the other hand, pure erythematous isolated lesions, without manifest evidence of exudation, are generally observed on the hard and sometimes the soft palate, this being attributed to the firm adherence of the mucous membrane in this situation to the underlying parts. In areas showing similar anatomical relations (pharynx, gums, vocal cords, etc.) [94] the pathologic alterations may assume the form of more solid elevations; papules, nodules and irregular tumor-like infiltrations. The hemorrhagic element is especially marked in lesions situated on the lips; it is common to find, as a result of the rupture of bullae, fragile crusts that often bleed on the slightest trauma.

It will be seen, then, that the characteristic cyanosed centers observed in the cutaneous lesions are apparently lacking in the enanthem. The latter also shows a greater tendency to form coalescent areas; this holds particularly in the case of the lips where one or more confluent patches may cover these parts. Annular figures and iris-formations are rarely encountered; when present, they are probably pathognomonic of erythema multiforme exsudativum.[49]

It is the rule for complete healing of the enanthem to occur, but relapses are common. There is also a marked tendency to recur, and instances illustrating several attacks in the mouth are common. It has been claimed that lesions may recur in the same areas and that local thickenings in the mucous membrane at these sites may result therefrom. This I have not yet had the opportunity of observing, but other writers have described this occurrence in what appear to be representative examples of erythema multiforme ex-

sudativum. It is important to stress that healing may occur in one area while the disease progresses in another; thus, the oral lesions may fade completely, while extension along the tracheobronchial tract takes place.

The foregoing description indicates how frequently the enanthem may present appearances simulating other dermatoses; in such instances the diagnosis must be deferred until such time as a more precise idea of the clinical course is obtained or other "revealing signs" appear.

B. Lesions in the Eye. Involvement of the conjunctiva, rarely the cornea, occurs more often than is generally supposed. Such instances were described in the older dermatologic literature,[60, 8, 37] but these represented mild cases in which the conjunctivitis was more or less regarded as an epiphenomenon. To v. Düring,[40] in particular, credit is owing for the first comprehensive account of this manifestation, observed by him in about three-fourths of 122 patients showing erythema multiforme exsudativum. The conjunctival lesions generally appeared several days after the onset of the exanthem, though occasionally they antedated it. There were more or less circumscribed symmetrical areas, about a millet-seed in size, situated in the bulbar conjunctiva on the line of opening of the lids, especially on the temporal sides. These spots were roughly triangular in shape, elevated, colored yellowish or light gray with a superimposed reddish tint, attributed to the presence of injected conjunctival and, perhaps also, subconjunctival vessels. The lesions were practically always bilateral. The remainder of the conjunctiva usually showed some degree of hyperemia. In other cases a catarrhal condition was superimposed, the patients complaining of burning, itching, tearing, mild photophobia and, occasionally, of a mucoid or mucopurulent discharge. The course was acute, healing occurring in from two to three weeks, without the production of residual changes. There were occasional local relapses that ran a similar course. Once keratitis was encountered, but this resolved completely. The outcome was, therefore, favorable in this group of patients. It was also observed that, when the cutaneous lesions affected the region of the eyes, the lids were swollen, notably the upper lids—an occurrence noted by many later writers.[67, 68, 45] Other investigators described a mild type of conjunctivitis in which, by the aid of a magnifying lense, small vesicles could be recognized,[69, 70] while still others mentioned coryza as one of the early symptoms of erythema multiforme exsudativum[37] or referred to banal forms of vascularization (hyperemia) of these parts.[71] Chevalier and Toulant[72] encountered an example showing a positive fluorescin test, despite which there was total restitution to normal, illustrating the essential benignity of the changes in this case; in addition, they found other alterations which they regarded as evidence of episcleritis. Instances showing conjunctival bullae were also occasionally observed, and the similarities to pemphigus of the eye were discussed. So far as the dermatologic literature was concerned, these were the most important changes described, and they were encountered in patients showing the papular or papulovesicular forms of erythema multiforme exsudativum, with or with-

out alterations in other mucous membranes. The prognosis for complete recovery was, therefore, regarded as excellent.

Simultaneously, however, severe examples of conjunctival and corneal involvement were observed, chiefly by the ophthalmologists who were consulted for these complications, occasionally by the pediatrician because many of the patients were children, and sometimes by the internist owing to the constitutional symptoms. In this manner, a rich literature containing abundant protocols was recorded, but the subject, instead of being simplified, became more complex, for now there were added a few new diseases and some patronymic titles. It is my intention to discuss these cases which appear to differ from erythema multiforme exsudativum and to attempt to show that they represent variants of this protean affection.

In discussing the problem it will be advantageous to begin, first, with a consideration of the milder examples and, then to lead, by a series of gradual transitions, into those instances presenting clinical pictures more difficult to classify.

a. Mild Cases. These manifest signs of a superficial "catarrhal" process. The eyelids are normal or moderately edematous. The palpebral conjunctivae are hyperemic and slightly hypertrophied; in more prolonged cases the bulbar portion is injected, glassy, and swollen with edematous fluid. There is increased secretion from the eyes, usually of a serous type, more uncommonly mucoid. In several examples under my observation the lids were pasted to the adjacent parts owing to the occurrence of a mucoid or mucopurulent secretion. Subjective symptoms are inconspicuous; at the most there may be smarting sensations and distress from the accumulation of exudative material. The course has a duration of from one to several weeks or longer. Healing occurs in the absence of important sequelae. Illustrative examples have been recorded in the older literature by Hanke,[73] Neumann [74] and Bergmeister [75] among others. In these cases the cutaneous manifestations were typical of vesiculobullous erythema multiforme exsudativum. In the first two instances cited, there were, in addition, characteristic lesions in the oral mucous membranes. Bergmeister's case is of particular interest owing to the many recurrences in the conjunctiva, absence of febrile reaction, and the occasional appearance of lesions in the eyes in advance of the exanthem. The more recent literature contains a number of examples showing somewhat more pronounced conjunctival lesions [54, 67, 70, 76]; of these the case recorded by Blair [54] merits particular interest, as it concerned a boy aged 12, in whom there were observed six separate attacks of the disease, with involvement of various parts of the integument. Related to this group are the numerous instances described by many other investigators under a variety of titles; these will be mentioned again in the section concerned with the lesions encountered in the miscellaneous mucous membranes.

b. Severe Cases. These take the form of "membranous or pseudomembranous conjunctivitis," affecting chiefly the palpebral portions and accom-

panied usually by a marked discharge of purulent or non-purulent nature; when the condition is more pronounced the intervening parts of the conjunctivae and bulbar portions are also affected. This division into variants is arbitrary, as there are transitional clinical pictures. Instances showing membranous or pseudomembranous conjunctivitis with few or no residual changes have been recorded by Fuchs,[42] Hanke (second case),[73] and Hartlev [77] among others; these were associated with typical oral and cutaneous lesions, and it is noteworthy that the course was afebrile in the examples reported by the first two observers cited. Next in severity were the instances described by Raffin [78] and by Stark [79]; in the first one, several white scars were found in the palpebral conjunctivae of the upper lids, while in the latter there were noted, some four years after onset, grayish deposits on the tarsal conjunctivae, nebulae, and clouding of the corneae. Barkan's patient [80] had residual chronic alterations causing ankyloblepharon, symblepharon, and corneal opacities producing blindness. Finally, at the opposite end in the scale are the cases reported by Stevens and Johnson,[29] Wheeler,[81] Rutherford,[82] Bailey [83] and Ginandes [84] among others; in these instances blindness was an outstanding complication during the acute phase of the affection. In some of the patients it was considered essential to remove an eye owing to fear of panophthalmitis. Practically all revealed evidence of oral and cutaneous lesions, and in some there was additional involvement of other mucous membranes. Deaths were recorded in the patients seen by Smith [85] and by Hanke,[73] the immediate cause being severe bronchopneumonia.

The Status of the Stevens-Johnson Syndrome

The group of cases showing severe ocular manifestations have been classified popularly under the category of Stevens-Johnson disease,[29, 84] the original belief being that this was a hitherto undescribed affection. Preliminary data have been furnished to indicate that these examples represent only a variant of erythema multiforme exsudativum, and the intention now is to complete the account with an analysis of a few features of special interest.

1. Age of Patients. Most of the cases showing severe or relatively severe ocular manifestations concerned children; young adults and occasionally older persons were also affected. Whereas, therefore, no age seems to be spared, it appears that children are apparently predisposed to the graver forms of the condition.

2. Cutaneous Lesions. Although occasional instances showed pure papular eruptions [81, 82, 83] or combinations of papular and vesiculobullous efflorescences,[73] the vast majority were accompanied by markedly exudative cutaneous lesions. Typical herpes iris of the skin was encountered in some cases,[42, 73, 75, 78] bullae with serous fluid in others,[77, 79] and hemorrhagic bullae in still others.[80, 84, 86] In several instances the dermatosis was generalized in extent and, in particular, covered the entire trunk.[73, 74, 81, 82, 83, 84] Occa-

sional cases showed rashes deviating from standard type, but conformity to textbook description cannot always be expected. To reject certain instances from this category because the thighs, for example, happen to be sites of predilection is to overlook natural variations in disease. Obermayer [87] and others have noted that in examples of erythema multiforme exsudativum affecting chiefly the mucous membranes, cutaneous lesions are apt to be encountered in atypical locations, as on the flexor surfaces (typus inversus). The crusting and "scaling" observed in some cases represented probably the sequelae of dried vesicles or collapsed bullae; the significance of these phenomena in erythema multiforme exsudativum has been previously discussed. Finally, recurrences have been met with in a number of cases,[29, 70, 75, 83, 88] and it is probable that the incidence of this feature would have been increased with greater opportunities for subsequent observation.

3. Ocular Lesions Alone. Hanke [73] recorded an instance of chronic membranous conjunctivitis (herpes iris of the eye), in which the lesions were restricted to that organ. In a condition with such protean manifestations this possibility may be conjectured. It is likely that study of the ocular alterations may reveal clinical criteria enabling the observer to diagnose the disease when limited to the eye, but this is a matter for future investigation.

C. Other Mucous Membranes. In addition to the parts already mentioned, other structures affected by erythema multiforme exsudativum are the nose, pharynx, larynx,[89] tracheobronchial tract, esophagus, glans penis, preputium, urinary meatus, urethra,* labia minora, vaginal tract,[90] cervix, anus and, perhaps, the lower end of the rectum. Of interest is the report by Brünauer [91] who observed a number of such eruptions showing marked predilection for the male genitalia, especially the scrotum; in principle, however, the lesions were similar to those already described. It has been stated that the entire gastrointestinal tract may also be involved, but this localization cannot be accepted without considerable reserve, as there are ample opportunities for confusion with the Osler-Henoch-Schönlein group (q.v.).

Of special importance are the many instances in which the affection remained localized to the mucous membranes. For example, Crocker [92] reported a case of bullous erythema multiforme affecting the oral cavity, without involvement of the skin; subsequently, during one of the attacks, erythema iris lesions appeared on the backs of the hands, and then the patient recalled a previous similar occurrence. Butler [93] described an example showing four recurrences of the vesiculobullous variety of the disease, with involvement of the skin and oral cavity; the fifth attack, which was febrile in type, was limited to the buccal, lingual and labial mucous membranes, the

* In a recent case under my observation a young physician had had several attacks of erythema multiforme exsudativum, sometimes with involvement of the mucous membranes. While in Switzerland, Dr. Bruno Bloch confirmed this diagnosis. The interesting feature was the occurrence of an intercurrent urethritis, the cause of which was not clarified. The relation of this phenomenon to erythema multiforme exsudativum was apparently never suspected, and it seems probable that some of the cases of non-specific urethritis may belong in this group.

integument having been spared. Such instances could be multiplied many times.

The Status of Ectodermosis Erosiva Pluriorificialis

The foregoing data support the belief that the cases reported under this title [28, 29, 30, 31, 32, 76, 95, 96, 97] merely represent variants of erythema multiforme exsudativum, characterized by preponderant involvement of the various mucous membranes, including the conjunctivae. Jausion and Diot,[98] reporting two examples of this syndrome, concluded that their cases, as well as those described by Fiessinger and his co-workers, belonged in the category of Bazin's [8] hydroa vésiculeux; the latter, according to the data in this paper, is one of the names used in France for vesiculobullous erythema multiforme exsudativum. In many cases there were cutaneous manifestations showing typical morphology; in a large proportion of instances recurrences were noted subsequently [28, 34, 76, 95, 96]; in others there were relapses [97]; and at least one observer stressed the seasonal incidence of the attacks.[95] My views are, therefore, in close agreement with the opinions expressed by Klauder [28] and by Kumer [96] who believe in the essential grouping of this syndrome under Hebra's erythema multiforme. The controversy between Baader,[34] who regarded his cases as representing a new entity, and Moncorps,[33] who classified the clinical picture as a "grippe" exanthem, is illustrative of the confusion that has crept into the literature when undue significance is attached to slight deviations from the normal or average textbook descriptions.

Systemic Manifestations

Thus far stress has been laid on those lesions on the basis of which the disease is chiefly recognized. In many instances the clinical picture is actually dominated by systemic features of more or less banal type, their occurrence tending to confuse rather than to clarify the diagnosis. During any individual attack of either papular or vesiculobullous erythema multiforme exsudativum constitutional symptoms may be absent; this is much less often the case in the latter type. There are, however, imperceptible transitions between the severe instances and those manifesting systemic features of minimal intensity; and, contrariwise, the papular variety may occasionally be accompanied by a pronounced constitutional reaction.

Prodromal Symptoms. A detailed study of erythema multiforme exsudativum reveals the protean nature of its manifestations, notably those occurring at the inception of the disease. Though it is common to describe prodromal symptoms, the order of appearance is irregular and unpredictable, depending on the severity, the extent and the particular system first affected. The early manifestations create the clinical impression of an "upper respiratory infection" in most instances, such patients complaining of one or more of the following symptoms: sore throat, bronchitis, laryngitis, irregular fever, nasal discharge, coryza, joint pains, slight headache, malaise, and oc-

casionally a lymphadenopathy of moderate degree. Thus, it becomes evident that in the early stages, before the appearance of characteristic lesions in the skin and mucous membranes, the clinical picture may closely resemble a host of other affections. In addition, the common prodromal complaints may also occur at the height of the disease or during any part of its course. For this reason it seems advisable to analyze the constitutional manifestations according to the system involved.

a. Upper Respiratory System. Antecedent angina is a common prodromal complaint, being usually attributed to the presence of lesions in the posterior part of the oral cavity or in the pharynx. In some instances, however, sore throat may precede the appearance of the exanthem or even the enanthem by as long a period as one or two weeks; at this time the condition may occur in the form of a simple red throat and, indeed, there may be hardly any objective evidence of local pathologic alterations. Although it is not rare to encounter cases showing a few asymptomatic lesions in the oral cavity, the presence of such efflorescences generally produces subjective symptoms moderate in intensity, occasionally pronounced. When the enanthem is widely distributed the outstanding features may be pain on ingestion of food, salivation, or dysphagia; the odor of the breath may be extremely fetid, as in pemphigus.

Involvement of the tracheobronchial tract and its finer radicles is generally accompanied by mild or severe bouts of coughing. It is in such instances that every nursing precaution must be utilized to overcome the possibility of a superimposed bronchopneumonia, especially in elderly people.

In rare cases the disease has been known to involve the esophagus, causing a sensation of burning localized roughly in that part. There are also recorded occasional examples featured by implication of the larynx; such patients generally show symptoms of transient acute laryngitis,[89, 94] but the complaints may vary from none in those revealing isolated lesions on laryngoscopic examination to marked interference in breathing in those having tumor-like plaques or ulcerated areas. It is probable that more thorough search at postmortem examination would yield a higher incidence of such lesions.

The nasal passages, especially the external nares, are often involved in this disease. There is usually local discomfort, mechanical difficulty in breathing, and a discharge that is serous, mucopurulent, tinged with blood, or frankly hemorrhagic due to traumatic detachment of superficial crusts.

Hemorrhagic or blood-tinged sputum is often encountered incidentally; it may result from pathologic changes in any part of the respiratory tract for reasons already outlined.

b. Fever. In the vesiculobullous variety of erythema multiforme exsudativum it is common to observe some increase in the temperature, occasionally a remittent type of curve, and in some cases the clinical picture of a severe febrile disease. The temperature may attain a height of 104° F. or even 105° F., and to this variant, characterized by pronounced constitu-

tional symptoms, Lortat-Jacob [25] gave the name "intense pyretic form" of erythema multiforme exsudativum. It must be stressed that occasionally the papular form of this affection may be attended by a severe febrile illness, though this is relatively uncommon. The irregularities in the temperature are so marked that it is difficult to speak of a typical fever curve, and this inconstancy is often betrayed in the variations exhibited in the relapses and recurrences. In many cases, especially in the erythemato-papular type, the temperature is normal, but too much reliance must not be placed on the subjective well-being of the patient, for in a few such instances I have been able to detect slight degrees of fever (up to 100° F.). It has been stated [36] that children afflicted with this affection are prone to manifest signs of an intense constitutional reaction; this rule, however, admits of many exceptions.

c. Articular Involvement. In many cases this manifestation is absent, but it is essential to question the patient carefully in an effort to discover the mild examples of this affection. When joint pains are encountered they are usually of the nature of arthralgias, designated more generally as "rheumatoid" or as "pseudo-rheumatic" for the purpose of differentiating them from true rheumatic articular disease. Evidence of periarticular involvement is uncommon, except apparently in cases where the small articulations are affected,[51] and still more rarely does an intra-articular effusion appear. I have not encountered any instance in which the fugitive, migratory polyarthritis characteristic of rheumatic fever in the corresponding age-group was truly simulated.

d. Involvement of the Heart. Cardiac murmurs are sometimes heard at the apex or the base of the heart, but in no instance under my observation did valvular defects result therefrom. The older statistics [15] on the incidence of endocarditis in this affection are unreliable, as they were compiled at a time when little effort was made to differentiate the host of diseases included under the generic title of erythema multiforme. Moreover, the diagnosis of organic valvular disease was based chiefly on the presence of a murmur at the apex or base of the heart, in many instances probably accidental or functional in nature. The essential point was recognized by Teissier and Schaeffer [99] who concluded that in many cases of "erythème polymorphe," these murmurs were "extra-cardiac" in origin; that the incidence of endopericarditis was very small; and that, contrary to the opinions expressed by Garrod [100] and by Lewin,[15] genuine valvular defects belonged to the rarities. It will be seen, from consideration of the data recorded in my various publications, that the discordance in views can be attributed to the different types of dermatoses studied, for Teissier and Schaeffer were probably concerned with erythema multiforme exsudativum; Garrod, in the main, with rheumatic erythema multiforme; and Lewin, with a heterogeneous group of conditions. No instance of erythema multiforme exsudativum has come under my observation, thus far, where electrocardiographic studies revealed significant alterations, this being equally true of the cases recorded by Meyer [101] under a different title. Fluoroscopic data are too meager, as

yet, to warrant drawing of definite conclusions, but this method of investigation should be employed more extensively.

e. Gastrointestinal System. My observations indicate that colic is neither a frequent nor a significant feature in erythema multiforme exsudativum; when this has been claimed, it seems evident that the affection has been confounded chiefly with the Osler-Henoch-Schönlein group, etc., etc. In one instance under my observation abdominal pain occurred, but this seemed to be caused by the coincidental presence of a painful ovarian cyst. Occasionally blood may be found in examinations of specimens of stool; this is generally caused by the swallowing of débris of superficially eroded lesions in the oropharynx, and nose; rarely, it results from lesions in the lower portion of the gastrointestinal tract. Under such circumstances the finding of a positive guaiac reaction in the stools is less significant, and this epiphenomenon cannot be regarded as the pathological equivalent of the process observed in the Osler-Henoch-Schönlein group of affections.

f. Urinary Tract. Involvement of the kidneys (inflammatory, degenerative or vascular) appears not to be an essential part of erythema multiforme exsudativum. I must therefore agree with Tachau [27] that the belief in the simultaneous occurrence of renal disease arose from the inclusion of many cases that do not properly belong in this category, for example, "systemic" lupus erythematosus.[4] When albuminuria is discovered it represents generally part of a febrile response or a coincidental finding. Hematuria, observed in occasional instances, is often caused by erosive inflammation of the urethral and preputial surfaces; this evidence per se cannot be regarded, therefore, as indicating involvement of renal tissue. By the same token, the occurrence of hypertension is probably coincidental and unrelated. The influence of renal failure on the morphology of other cutaneous lesions has been discussed in a previous section.

g. Lymphadenopathy. Generalized enlargement of the superficial lymph nodes is sometimes encountered,[12, 45, 138, 153] but it rarely attains an extreme grade.[12] When present, the glands are usually moderately enlarged. Düring [40] observed enlargement of the cervical nodes in an appreciable percentage of his cases; this is to be expected in instances showing secondary infection in the oral lesions. It is to be stressed, however, that lymphadenopathy may be encountered in the absence of such complicating factors. In one instance under my care the right pre-auricular node reached the size of a large bean, the remainder of the superficial lymph glands being smaller, though palpably enlarged. I have also observed several examples in which the lymphadenopathy was sufficiently pronounced to suggest the possibility of infectious mononucleosis. It is probable that occasional instances may show involvement of the hilar glands [153, 102]; for example, Liebner [102] found hilar shadows in four out of 15 cases of erythema multiforme exsudativum. The precise significance of these findings is, however, still uncertain.

h. Splenomegaly. Moderate enlargement of the spleen is sometimes encountered.[21, 40, 45] This I observed once, the organ being felt, as a mod-

erately firm structure, about one finger's breadth below the costal margin; with resolution of the disease the spleen receded.

i. Blood Findings. In the average afebrile case there are no definite abnormalities in the blood-count. In the intense pyretic form and in the presence of such complications as bronchopneumonia there are variable degrees of leukocytosis, with an increase in the polymorphonuclear leukocytes. Eosinophilia is an uncommon coincidental finding. In a few instances, as in two cases under my observation, there was a moderate degree of leukopenia with relative lymphocytosis; the occurrence of palpably enlarged lymph nodes suggested the possibility of infectious mononucleosis, but the heterophile reaction was negative. Mild secondary anemia occurs occasionally, and there are no significant alterations in the blood platelets. In a few instances I have observed a local eosinophilia in bullous lesions, but the banality of this phenomenon depreciates its significance for diagnosis. There are many cases showing marked variability in the blood-counts made during the initial attacks and in the recurrences. In summary, the findings in the blood seem to shed but little light on the nature of the affection.

Prognosis

Hebra [9] emphasized the benign nature of the disease, though he had seen one case terminate in pneumonia. There are observers, among whom Tachau may be mentioned, who deny the occurrence of severe complications as an essential part of the affection and therefore reject the so-called malignant form of erythema multiforme exsudativum. It is undoubtedly true that numerous lethal cases have been classified erroneously in this category when, in reality, they represented examples of acute "systemic" lupus erythematosus, "capillary toxicosis" of Frank, and other conditions. Nevertheless, I have seen fatalities occur in a number of authentic cases of erythema multiforme exsudativum, owing to: (1) bronchopneumonia secondary to aspiration of decomposed and infected material in the oropharynx, notably in elderly people; (2) simultaneous involvement of the tracheobronchial tract with superimposed bronchopneumonia; (3) an intercurrent complication which may be related only in the sense that there is lowering of the patient's local or general resistance; (4) perforation of the eyeball, when the conjunctiva and cornea are intensely affected, leading to panophthalmitis and, perhaps (?), secondary invasion of the blood stream, especially in children. Blindness in one or both eyes, partial or total, represents the most common complication in these cases.

These data, therefore, indicate that the prognosis depends essentially on the degree of involvement of the various mucous membranes. In the vast majority of cases recovery is the rule, despite the clinical impression of severe toxemia in some instances. This point was well illustrated in the five examples of this disease reported by Eisenstaedt,[53] recovery ensuing though the patients seemed to be desperately ill. In rare instances of the severe form of the disease there may be encountered psychotic manifestations [68, 138]; in at

least one case,[68] a man of 20, the patient recovered completely from the attack. The essentially benign course of the affection is shown especially in those instances manifesting seasonal recurrences.

Essential Differences between Tachau's Account and the Data in This Paper

In summarizing the controversial aspects of this subject, it seems pertinent to indicate briefly the outstanding points of debate; in this manner fundamental distinctions are likely to stand out in bold relief, and such differences may serve as the basis of further investigation. The most representative of the numerous European publications concerned with this subject is that of Tachau[27] who adheres to the views held by the old Vienna school. To summarize the essential points of dissimilarity:

1. Tachau does not admit the occurrence of fatalities and even denies the authenticity of cases illustrating a severe clinical course. The data recorded in this paper appear not to substantiate this fundamental contention.
2. Tachau, although admitting the occurrence of microscopic extravasations of red blood cells, denied the possibility of gross visible hemorrhage into the lesions. It is my belief that such an absolute statement is not justified.
3. Tachau's account of the lesions in the eyes is confined to the mild manifestations, the implication being that the severe cases belong to another category of disease. The data recorded in this paper are at variance with the above belief. In arriving at this conclusion I have followed Tachau's rule that atypical manifestations are to be regarded as part of the affection only if observed with some regularity in association with typical features of erythema multiforme exsudativum.
4. It is, therefore, understandable that Tachau differentiates the clinical pictures described by Fiessinger and by Baader from that seen in erythema multiforme exsudativum. This point of view seems unacceptable for the reasons already mentioned in the paragraphs devoted to a consideration of these syndromes.

Differential Diagnosis

The outstanding diagnostic features are revealed by the lesions in the skin and mucous membranes. The systemic manifestations are, on the other hand, banal; yet, it is essential to recognize them, if only for their negative attributes. At this point two legitimate questions may be asked. (1) Can erythema multiforme exsudativum be diagnosed solely on the basis of a single or a few cutaneous lesions? In such instances it appears that this disease may be strongly suspected provided the morphology of the individual efflorescences corresponds to the descriptions already furnished, but it is wise to suspend judgment until such time as the clinical course can be better evaluated. (2) Are the mucosal lesions recognizable per se? While

there are observers who may be inclined to doubt this and while it is true that these manifestations may be simulated closely by a host of other affections, it is my belief that erythema multiforme exsudativum confined to the mucous membranes, especially of the mouth, may be recognized in a high percentage of cases on the basis of the appearances exhibited in these parts and the concomitant general clinical picture. When the disease has an acute onset and short duration there may be genuine diagnostic difficulties that are generally overcome, however, by further observation.

It is my intention in the ensuing section to restrict the discussion of the differential diagnosis to the affections that I have encountered in private practice, dispensaries and medical wards.

1. Rheumatic Fever. Throughout the history of erythema multiforme exsudativum the question of "rheumatism" has loomed large owing to obscurities in conception and nomenclature. At the outset it may be noted that the cutaneous lesions in rheumatic fever rarely, if ever, show a vesicular, pustular or bullous component; in the excessively rare instances where such phenomena were described, the diagnosis of rheumatic fever was doubtful or the rash could be attributed more properly to another cause.[3] On the other hand, erythema marginatum rheumaticum presents certain resemblances to the marginated form of erythema multiforme exsudativum. The former differs, however, in its more rapid onset; striking predilection for the trunk; remarkable changes in configurations within short intervals of time, generally measured in hours, occasionally in days; occurrence in successive crops over days, weeks or even longer; appearance chiefly in children; and in the association with rheumatic stigmas, such as organic cardiac disease, subcutaneous nodules and chorea. This subject is discussed in greater detail in another place.[3]

2. Erythema Nodosum. The average example of erythema nodosum shows distinctive cutaneous lesions and clinical course. The mucous membranes are spared, though in a number of instances I have seen the eyes affected in the form of wedge-shaped episcleritis as well as milder examples of what is commonly described under the broad title of "phlyctenular conjunctivitis"; these lesions were essentially benign and disappeared without leaving sequelae. A few observers have apparently noted involvement of the oral mucous membranes in the form of erythematous nodules, but such manifestations belong to the curiosities of medicine. I have not encountered any instance of severe conjunctival or corneal lesions simulating those found in erythema multiforme exsudativum. Occasional writers have observed hemorrhagic efflorescences under the nail plate (Verco's sign) in erythema nodosum. It is of interest that similar lesions were found by Scheremetjew [103] in a case of "polymorphous exudative erythema," featured by an eruption on the face, backs of the hands, external aspects of the legs; fever; recurrent crops of what was interpreted as erythema nodosum of the legs; glands in the neck, submaxillary, axillary and inguinal regions; joint pains, etc., etc. It is, however, exceedingly difficult to classify this instance

in a precise category, and substantiation of this observation awaits further study in fresh cases. The common finding of enlarged hilar nodes ("hilitis") in erythema nodosum is probably also duplicated in erythema multiforme exsudativum,[102] though to a much lesser degree; it is, therefore, difficult to be certain of whether this can be used as a differentiating feature, the more so as roentgenograms of the chest are more often taken in the former affection in view of the prominent part played by the tuberculous theory of erythema nodosum, whereas such studies are but rarely pursued in erythema multiforme exsudativum. Nor am I certain that a marked tuberculin reaction, even in graded dosage, is sufficiently characteristic to distinguish these diseases. These points, among others, require further investigation for precise evaluation.

The differential diagnosis between these affections becomes confusing under the following uncommon circumstances. (1) There are cases of genuine erythema nodosum accompanied by lesions on the face and other parts, where exudative attributes (especially vesiculation) are occasionally observed; of this variant I have encountered two striking examples, and others, such as Adamson, have recorded additional examples. (2) Erythema multiforme exsudativum may be accompanied by lesions on the lower limbs, where, owing to the influence of anatomical peculiarities, these efflorescences are apt to be somewhat nodular, to show a cyanosed hue and to reveal tenderness on palpation. This point has already been elaborated in a previous section in which it was also noted that these attributes are manifested by a large number of dermatoses. It is this type that is often described as erythema multiforme exsudativum combined with erythema nodosum. Despite these occurrences it would be unwise at present to regard the febrile forms of these affections as identical without further study of so-called transitional examples. In the section devoted to the resembling forms of tuberculides of the skin there will be described an eruption that has been confused occasionally with these "transitional" cases. In its classical form, erythema multiforme exsudativum is a well-characterized disease that differs radically from idiopathic erythema nodosum in the location, morphology and clinical course of its cutaneous and mucosal manifestations.[39]

3. Osler-Henoch-Schönlein Syndrome ("Capillary Toxicosis" of Frank). It will be remembered, as a point of historical interest, that Osler in one of his earlier papers on this subject used the term erythema multiforme exsudativum to describe the cutaneous manifestations. While the eruptions encountered by him were truly polymorphous, it is a tribute to his clinical ability that he later dropped this term and substituted for it the more non-committal name of "erythema group." In several other publications [1, 4, 104] I have discussed the conception of this affection and have presented data indicating that the clinical pictures described by Schönlein, by Henoch, and by Osler appear to fall into a single category corresponding essentially to "capillary toxicosis" in the sense of Frank. The average example of this affection presents distinctive cutaneous and internal medical

features. In comparison with these lesions involvement of the mucous membranes, including the eyes, is comparatively uncommon, though important for reasons that will be mentioned in another publication. It is not my intention, at present, to describe the various polymorphous rashes associated with capillary toxicosis, but rather to restrict the discussion to the so-called "erythema multiforme-like" type of lesions (erythematous papules) commonly observed in the affection, as this is the variety most likely to be confused with erythema multiforme exsudativum.

In capillary toxicosis the cutaneous lesions show a striking propensity to affect the areas about the joints (in the order of frequency: ankles, knees, elbows, wrists, hips, shoulders, etc.), although outlying parts may also be involved, and, least commonly, the trunk and face. As there are occasional instances of erythema multiforme exsudativum exhibiting eruptions confined, for the most part, to similar areas, the differentiation would be difficult, were it not for the succeeding alterations that endow the lesions in capillary toxicosis with recognizable peculiarities. Thus, even early in the course there is a secondary hemorrhagic component which is often superimposed in the form of a central punctum, or as a minute hemorrhagic vesicle; or, what is more characteristic, subsequent crops of frank purpuric and petechial spots may entirely replace the "multiform" lesions, with similar favor for areas about the joints. Additional help is, moreover, afforded by the nature of the internal medical manifestations, the clinical picture being dominated often by two distinguishing features: (1) evidence of genuine renal disease, the nature of which will be discussed in another publication; (2) gastrointestinal symptoms pointing to involvement chiefly of the areas about the ileocecal valve. It must be stressed, however, that the finding of blood alone in the urine and in the stools is not necessarily clear-cut evidence of "capillary toxicosis," as this may be encountered occasionally in erythema multiforme exsudativum for reasons previously mentioned. I cannot, therefore, agree with Glanzmann in the classification of the third case described in his paper (1928) [105] as an example of erythema multiforme exsudativum, but, on the contrary, believe that the clinical features in that patient pointed clearly to the Osler-Henoch-Schönlein group (sore throat, fever, joint involvement, typical location of the crops of petechiae, intermittent attacks of colic, many bloody stools, etc.).

Finally, although spontaneous recovery appears to be the rule in "capillary toxicosis" and while the affection seems not to be nearly as grave as one would be led to infer from accounts in the literature, the prognosis, nevertheless, should be guarded in all instances. This holds especially for those cases characterized by evidence of severe renal or gastrointestinal involvement. A small, though definite, percentage of cases, estimated roughly at from 10 to 15, end fatally. The most important causes of death are: (1) renal insufficiency; (2) intussusception; (3) perforation of the small intestine leading to peritonitis; (4) intercurrent infections (especially in the rare instances affecting the mucous membranes) and unrelated infections that are

probably not an essential part of the disease, but rather represent a sequel to lowering of the patient's local or general resistance; the former event occurred in one striking case under my observation where secondary infection of hemorrhagic oral lesions played a notable part in causing a fatal issue. Considered in terms of the composite clinical picture, the differentiation is difficult only in occasional instances.

4. Systemic Lupus Erythematosus. The well-developed case of systemic lupus erythematosus shows a multiplicity of distinctive cutaneous and internal medical features that may be regarded as practically pathognomonic of this disease. A more complete account of these manifestations will be found in several other publications,[1, 4, 106, 107, 108] and to these data I have added, in the appropriate sections in this article, additional points relative to simulating eruptions encountered in a large number of instances of erythema multiforme exsudativum, particularly in its vesiculo-bullous form. As the subject will receive more detailed consideration in a forthcoming monograph, this section will be concluded with mention of two interesting points. (1) There are cases which are diagnosed in the early stages as erythema multiforme, owing to the occurrence of lesions situated chiefly on the extensor aspects of the limbs, which subsequently develop the full-fledged picture of systemic lupus erythematosus. In some cases this differentiation is indeed difficult, but a relatively short period of observation generally suffices to resolve this problem. (2) The factor of coincidence must always be taken into consideration; for example, drug rashes simulating erythema multiforme exsudativum may in rare instances complicate a preëxistent lupus erythematosus. It is essential, therefore, that every case be evaluated meticulously and that coincidental factors be relegated to their proper place.

5. Bacteremia. In a recent publication Bingold [109] discussed the problem of erythema multiforme exsudativum in connection with dermatoses encountered in the course of various types of bacteremia. Whereas "septic" eruptions may be considered broadly as polymorphous in their clinical attributes, the resemblances between them and erythema multiforme exsudativum are, in my opinion, based on superficial analogies. For example, gonococcal bacteremia is occasionally accompanied by a peculiar type of rash displaying multiformity in the cutaneous lesions, and hence called "erythema multiforme"; my observations [2] indicate that these efflorescences, which are caused by the gonococcus, may be differentiated with comparative facility in most instances from erythema multiforme exsudativum, and in advance of a positive culture of blood. This is particularly true if the clinical attributes of the rash are correlated with the internal medical manifestations. This observation leads inevitably to the principle, recognized by Bingold and others in a preliminary way, that the various types of bacteremia are often accompanied by highly characteristic eruptions, and that recognition of these cutaneous lesions may enable the observer to diagnose not only the presence of bacterial invasion of the blood stream, but also, in many cases, the nature of the causative organism. It is my intention, in the future,

to furnish evidence substantiating this principle. Before concluding this section, it may be mentioned that there are occasional instances of chronic meningococcemia featured by the appearance of erythemato-vesicular lesions on the upper limbs and elsewhere and that these may be confounded with the exudative variety of erythema multiforme exsudativum. This mistake I once made in a peculiar instance, and the lesson I learned was that in any patient exhibiting an atypical erythemato-vesicular eruption, associated with rises in temperature resulting in a prolonged intermittent or remittent febrile course, numerous attacks of polyarthralgias, and a remarkably good state of health despite the protracted course, the possibility of chronic meningococcemia should be given serious consideration. The importance of such a differentiation will be discussed in my publication dealing with the eruptions observed in the various types of bacteremia.

6. Fuso-Spirochetal Disease. The subject of Vincent's (fuso-spirochetal) disease is at present in a confused state, owing chiefly to the lack of genuine diagnostic criteria for its recognition. To classify a condition in this category on the basis of painful stomatitis associated with the finding, in a smear, of fusiform bacilli and spirochetes, even in large numbers, must inexorably lead to important errors in diagnosis. For example, I have encountered a number of cases in which these criteria were fulfilled, yet these concerned instances of leukemia in its acute phase, pemphigus, uremia, erythema multiforme exsudativum, etc. It is evident, from a critical perusal of the literature, that many unrecognized examples of erythema multiforme exsudativum are being labeled as Vincent's stomatitis with cutaneous lesions on the basis of doubtful criteria, as a result of which the remedy used in the particular case has come in for undue praise. Without analyzing the data in great detail, it seems likely that what at present may be termed primary fuso-spirochetal disease of the mouth (necrotic gingivitis and its variants) appears to be a fairly well-defined entity,[110] featured by (1) typical localization of the lesions; (2) fairly characteristic subjective symptoms and objective signs in the acute and chronic stages; (3) definite response to oxidizing agents in most cases, and, perhaps also, to the arsphenamines in severe instances. There is urgent need for close coöperation of dentists, internists, dermatologists, and bacteriologists for the purpose of more precisely determining adequate clinico-pathologic criteria for the recognition of Vincent's disease and its related affections. It is a subject that should be investigated from the ground up and nothing assumed as true unless substantiated beyond a reasonable doubt.

7. Pemphigus. The differential diagnosis between erythema multiforme exsudativum and pemphigus may be exceedingly difficult, if not impossible, in the early stages and in cases featured by restriction of the process to the oral and other mucous membranes. There is a popular notion that recovery points indubitably to the former disease and death to the latter, but this rule has numerous exceptions, particularly if it is applied to single attacks; temporary "cures" probably occur in pemphigus and fatalities may supervene

in erythema multiforme exsudativum. Ocular involvement of the nature of essential shrinkage of the conjunctivae may appear in both affections and, probably also, in other diseases, though the condition is most commonly encountered in pemphigus. Early in the course a few aberrant bullae in erythema multiforme exsudativum may be lacking in the usual erythematous halo, and, contrariwise, it is not unusual to observe an inflammatory reaction about isolated lesions in pemphigus of the skin in advanced stages. The age incidence, the Nikolski sign (detachment and fragility of the superficial epidermis following the trauma of rubbing the skin), and the phytotoxic test (Pels-Macht) are probably not decisive in judging individual instances or in establishing an absolute diagnosis. There may be an exception to the preceding statement in that pemphigus is much less likely to affect young adults, though there are probably exceptional examples. Histologic examination often provides differential diagnostic data, but whether this is also true in atypical cases cannot be stated with confidence at present. The common complications and causes of death in erythema multiforme exsudativum have been mentioned in the section on prognosis; in pemphigus fatalities result generally from bronchopneumonia, "toxemia," exhaustion or "cachexia," terminal bacteremia and other complicating infections such as tuberculosis,[111] and, rarely, perforation of gastrointestinal ulcerations. There are, however, many examples where even a complete postmortem examination fails to shed light on the cause of death or to furnish the slightest information on the nature of the essential process.

It follows, then, that there are occasional instances in which these diseases cannot be distinguished on the basis of the observation of a few lesions, and a probable opinion can be formulated only on a consideration of the attributes shown by the composite eruption and the general clinical course. In most cases, however, these processes are fairly distinctive; it is essential always to eliminate the possibility of drug eruption. I have seen a number of patients presenting oral lesions, concerning which opinions fluctuated between the diagnosis of erythema multiforme exsudativum and pemphigus; the vexing problem was finally resolved by the subsequent appearance of the cutaneous efflorescences characteristic of the respective diseases. Chronicity in the evolution of individual lesions is a feature encountered consistently in pemphigus, and this property is especially seen in the case of efflorescences situated in the integument. A history of preceding weakness, poor health, marked loss of weight, etc., prior to the appearance of the exanthem or enanthem point in the direction of pemphigus, but each case must be individualized.

According to Kinnear [112] and Levin, Tolmach and Schweig,[113] there is a variety of pemphigus vulgaris exhibiting the features of "erythema multiforme." I submit, on the basis of the data previously described, that no convincing proof has been offered in substantiation of this thesis; that this view is based on a paucity of atypical examples diagnosed on the basis of doubtful criteria; that, included in this group, are some typical instances of

erythema multiforme exsudativum, as in Kinnear's paper; and that, to repeat, death does not necessarily mean pemphigus, and recovery does not necessarily mean erythema multiforme exsudativum.

8. Foot-and-Mouth Disease. Occasionally, as in several instances under my observation, the oral lesions in erythema multiforme exsudativum may be accompanied by hemorrhagic bullae situated about the nails, and, in such circumstances, the occurrence of foot-and-mouth disease may be suspected. The virus of this affection was apparently first demonstrated in 1920 by Waldmann and Pape who used the guinea pig as the experimental animal. Before this, foot-and-mouth disease could be suspected only on the basis of clinical and epidemiological evidence, and the factor of coincidence was hardly appreciated. In one example of erythema multiforme exsudativum Klauder [28] was unable to demonstrate the virus by the standard procedure of inoculating the serum of vesicles into scarified areas on the plantar surfaces of a guinea pig. Recently, Richter [114] recorded a probable example of foot-and-mouth disease in a man 34 years of age, in whom the affection appeared two days after the ingestion of raw milk, but in view of the atypical clinical features and the atypical results in the inoculation of a guinea pig, it is difficult to be certain of the diagnosis in this case. The present status of the subject has been admirably summarized by Martland [115]: "A differential diagnosis cannot, however, be made with certainty on clinical grounds alone. All suspected cases should be confirmed by infecting a susceptible animal and demonstrating the nature of the virus by cross-immunity tests. Not all cases reported as foot-and-mouth disease have fulfilled these criteria; the majority were recorded before the guinea pig was recognized as an experimental animal in this connection. Many are, therefore, open to doubt, particularly those cases which had cutaneous lesions on areas other than the soles and palms in which the lesions continue to develop for a prolonged period. Foot-and-mouth disease in man is probably a comparatively rare occurrence. Transmission from man to man has not been demonstrated." It is clear, then, that the utmost circumspection is required in the investigator who diagnoses this condition in man, and no case can be regarded as belonging in this category without the direct substantiation of animal experiment and cross-immunity tests.[116]

9. Dystrophic Epidermolysis Bullosa. The dystrophic type of epidermolysis bullosa may occasionally simulate erythema multiforme exsudativum. In both there are encountered bullae in the skin and mucous membranes. In the rare instances showing involvement of the ocular structures with the production of "essential shrinkage of the conjunctivae," the differential diagnosis may be most delicate. In general, however, dystrophic epidermolysis bullosa exhibits the following distinguishing features: (1) inception of the process in early childhood; (2) familial occurrence of the disease which is handed down as a recessive character; (3) the concomitance, sooner or later, of dystrophic nail changes; these are practically always associated with alterations in the mucous membranes; (4) the frequent healing with

the formation of atrophic or scarred areas in the skin and oral cavity; the formation of milia or pseudo-milia is a common sequela that is, however, not pathognomonic; (5) the origin of lesions at sites of pressure and their frequent reproduction by mechanical traumas; (6) the appearance of hemorrhagic bullae. In typical examples the clinical picture is distinctive. In the past too much reliance has been placed on the finding of diminished or absent elastica fibrils in microscopic sections of affected and unaffected skin, but the technical difficulties in staining, the discordance in the histologic interpretations, and the lack of adequate controls are a few factors that warrant circumspection in evaluating this type of evidence.

As stated, the cases showing involvement of the eyes are the ones presenting the closest similarities to erythema multiforme exsudativum. A review of the literature bearing on this phase of the subject reveals that, whenever complete clinical details were furnished, the case was of the dystrophic type,[117, 118, 119, 120, 121, 122] rather than the simple form of epidermolysis bullosa (nails affected in nearly all cases, familial occurrence of the disease, inception at an early age, etc., etc.). The few exceptions to this rule are the examples recorded by Bogrow [124] and by Cohen and Sulzberger [123] and it is precisely in these instances that the diagnosis of epidermolysis bullosa, though probable, was not absolute. Thus, in the case described by Sulzberger and Cohen, an instance which I had the opportunity of observing several times without being able to classify it precisely in my own mind, the aforementioned features of typical dystrophic epidermolysis bullosa were generally lacking. This was also true in the example recorded by Bogrow [124] and, indeed, this observer apparently had doubts in his own mind as to the classification of this instance. In both cases there were cutaneous lesions that simulated strongly those seen in erythema multiforme exsudativum. It suffices to state, then, that in contradistinction to Duke-Elder's account,[125] these atypical examples must not be regarded as proved beyond cavil. Essential shrinkage of the conjunctivae seems to be a syndrome caused by several affections, of which the most common are pemphigus, epidermolysis bullosa, erythema multiforme exsudativum and, perhaps, other diseases. It must be admitted, however, that " cicatricial atrophy " and the resultant secondary trichiasis are probably encountered more often in dystrophic epidermolysis bullosa than in erythema multiforme exsudativum, though these pathologic alterations are not absolutely distinctive. It is evident that a renewed interest in the ocular lesions observed in these diseases is essential before more precise interpretations can be offered.

10. Drug Eruptions. In another publication [39] I have discussed some of the difficulties encountered in differentiating drug eruptions from erythema nodosum; here it is my intention to mention a few principles that hold analogously in the case of erythema multiforme exsudativum.

A variety of drugs may produce eruptions that fall within the bounds of the broad definition of erythema multiforme as given in the first part of this paper. With occasional exceptions such rashes do not resemble closely

that which is seen in erythema multiforme exsudativum. A classical example illustrating this point is provided by Abramowitz's original report [126] in which "fixed eruptions" were classified under the title of erythema multiforme; several years elapsed before Wise and Abramowitz [127] recognized the etiologic factor (phenolphthalein) in these cases. It may now be said that the appearances presented by this dermatosis are generally so distinctive that the diagnosis of drug rash suggests itself almost at a glance; on the other hand, further observation has revealed similar "fixed eruptions" caused by antipyrin, arsphenamines, veronal and other substances. In other words, additional knowledge has aided in separating these dermatoses from the vague inclusive category of "erythema multiforme."

On the other hand, the enanthems produced by drugs may present almost insurmountable difficulties in the differential diagnosis from erythema multiforme exsudativum, especially in cases featured by the restriction of the lesions to the oral cavity. A cardinal rule, then, is to eliminate the former etiology in all such instances, whenever possible. This requires generally a complete and critically evaluated history in addition to consideration of the features of the enanthem and of the associated collateral aspects. The complexity of the subject, as revealed by study of isolated instances, precludes further discussion in this paper.

11. Miscellaneous Affections. In the course of this study there were encountered simulating eruptions in a variety of diseases, such as pneumonia (especially in the stage of resolution), neoplasms (particularly in the deep-seated types subjected to radiotherapy), pernio, "purpura urticans" (?), infectious mononucleosis, periarteritis nodosa, dermatomyositis, etc., etc. On the other hand, examples of erythema multiforme exsudativum were observed in which the clinical features resembled measles, varicella, and infectious mononucleosis, in addition to the other affections considered in previous sections. Other observers have seen what seem to be resembling rashes following vaccination, sensitivity to light, diphtheria, cholera, and trichophytosis among many other conditions, and in the older literature erythema multiforme exsudativum was often confounded with hemorrhagic variola. It is probable, also, that Haverhill fever represents a separate entity, judging on the basis of the available reports.[128]

These eruptions, which are at present designated as "toxic erythemas," deserve renewed study, and it is my belief that future investigations will disclose criteria enabling the observer to recognize the rash with greater precision.

The section will be concluded with a brief consideration of the alleged relation between erythema multiforme exsudativum and the two diseases, tuberculosis and syphilis.

12. Tuberculosis and Erythema Multiforme Exsudativum. That eruptions designated roughly as erythema multiforme may be encountered in patients suffering from active tuberculosis seems probable, for neither disease appears to confer an immunity against the other. However, Ramel's

claim [129] that erythema multiforme exsudativum is of tuberculous nature requires careful consideration; this observer believed that he had demonstrated such an origin by using the method of multiple inoculations into guinea pigs. The reliability of this procedure and related investigations has been seriously questioned by some from the point of view of pure bacteriology; moreover, a few observers,[130] utilizing the technic advocated by Ramel, have been unable to substantiate the latter's results. At present there are reasonable grounds for concluding that decisive bacteriologic evidence indicating an alliance between these two affections is still lacking.

Clinically, however, occasional examples of "erythema multiforme" may be encountered in apparent relation to an active tuberculous process. Thus, there came under my observation an instance of tuberculous intracanalicular bronchopneumonia and meningitis in a child who showed symmetrical patches of erythema about the extensor aspects of the ankles and knees. This type of nondescript erythema is often classified as "toxic erythema" or as "erythema multiforme," both terms being employed in the broadest sense possible, and in this particular patient the precise relation between the cutaneous lesions and the tuberculous process remained obscure (toxic?, bacterial?). Of greater importance for the problem under consideration is the occurrence of a more acute variety of erythema induratum revealing transitions of papulonecrotic tuberculides and resembling either erythema nodosum, erythema multiforme exsudativum or combinations of these rashes.[39, 131] Of this variant I have had the opportunity to study three striking examples, characterized by the occurrence of cervical lymph node tuberculosis, typical papulonecrotic lesions, and painful, purplish red, nodular efflorescences on the lower limbs. The latter simulated ordinary erythema nodosum, the resemblances being further promoted by the failure to ulcerate and the assumption of an intense purple hue in the course of gradual involution. They differed, however, in their longer duration, in their association with typical lesions of papulonecrotic tuberculides (some of which failed to show the characteristic central necrosis), and in the presence of chronic active tuberculosis of the lymph gland variety. In some instances the necrotic centers may be so small and superficial as to create the effect of dried vesicles, and as the lesions may be situated on the dorsum of the hands and the extensor aspects of all the limbs, and as they may recur in many crops, the eruption often takes on features simulating Hebra's erythema multiforme exsudativum. Peculiarly enough, the three cases mentioned concerned women of middle age and beyond; all had subfebrile temperature during some part of the course, and all recovered, at least temporarily. Two of them were followed for many months; of these one had a draining sinus in the neck, which apparently healed after the use of ultraviolet and roentgen-ray irradiation, though this required a long time. However, almost one year later I ascertained that the cutaneous lesions had recurred on several occasions. Similar cases have been recorded by other writers under

a variety of titles,[132] and it seems probable that this syndrome is more common than is indicated by the paucity of reports concerned with it.

13. Syphilis and Erythema Multiforme Exsudativum. In 1903 Hoffmann [133] recorded 13 examples of secondary syphilis associated with lesions interpreted as erythema nodosum, erythema multiforme exsudativum, or both; of these, two had erythema multiforme exsudativum alone, while in three other cases this eruption was combined with erythema nodosum. In another publication [39] the present views regarding the alleged syphilitic etiology of erythema nodosum have been discussed, and here it is proposed to confine the remarks to a consideration of the corresponding status of Hebra's erythema multiforme. In some of Hoffmann's patients vesicular and "pustular" lesions were encountered; the rarity of a vesicular component in acquired syphilides need only be mentioned.[134] Subsequently, Lesser [135] opined that the simultaneous appearance of erythema multiforme and erythema nodosum indicated a syphilitic origin, but this has not been substantiated by observations made in the Wassermann-test-era, and it seems likely that this particular view is in need of critical examination. In perusing the data found in the older literature, it appears that there were three sources of difficulty:

1. Confusion of the mucous membrane lesions of erythema multiforme exsudativum with those of syphilis, an occurrence that is by no means rare. Trautmann [136] collected a large number of instances illustrating the point. Of special interest was the remarkable case described by Lau,[137] in which recurrent attacks of erythema multiforme exsudativum were repeatedly treated as syphilis. Nor was this confusion restricted only to the simulating lesions in the mucous membranes, for Besnier and Doyen,[12] Kaposi and others had observed instances of erythema multiforme exsudativum resembling cutaneous syphilis and Grindon "had seen several cases of so-called bullous syphilides presented at medical societies, which upon investigation proved to be herpes iris."
2. Complete reliance on a therapeutic test which in any disease of short duration may lead to "therapeutic fallacies" unless carefully controlled.
3. Insufficient attention directed to the possibility of drug etiology (iodides, etc.), notably in the older reports.
4. To these sources of error may be added a fourth which operates at the present time, namely, the finding of a coincidental positive Wassermann reaction. This I encountered once in a probable example of erythema multiforme exsudativum occurring in a patient with latent syphilis; the rapid disappearance of the rash without the aid of anti-syphilitic treatment argued in favor of these affections being coincidental and unrelated.

On the other hand, there are occasional instances of secondary syphilides presenting, at inception, attributes that simulate erythema multiforme in its broadest sense. Twice I have encountered such eruptions situated chiefly on the abdomen and marked by what appeared to be a pronounced urticarial component (edema?) superimposed on relatively bright-red papules, without accompanying subjective symptoms. It is curious that these two patients had complaints referable to the rectum. Physical examination showed painful fissures in ano, these lesions representing in reality defects in surface continuity of syphilitic chancres. This was recognized in one case after operative intervention was unavailing, and a subsequent Wassermann test was positive (four plus); in the other instance a routine Wassermann test proved to be the revealing sign of an obscure complaint, the patient finally admitting to the practice of pederasty. In these examples there was little likelihood of "erythema of the ninth day" (Milian),[139] as the eruption appeared before the institution of anti-syphilitic treatment. The opinion has been advanced by Ehrmann [140] that erythema multiforme-like lesions in secondary syphilis are not of specific origin, but due to syphilitic tonsillitis which allows multiplication of common bacteria with absorption of their toxins. This interesting belief did not hold in the two cases cited, as sore throat was not a complaint and oral manifestations were absent; and whereas an analogous theory can be held for the rectal lesions, this hypothesis, though reasonable, remains unsubstantiated.

Etiology

In 1860 Hebra [9] confessed his ignorance regarding the cause of this disease when he wrote: "These erythemata are often ascribed to catching cold, or to errors in diet, or to mental emotions; but unless the real existence of these conditions can be proved, I regard such expressions as mere commonplaces and shibboleths; and, rather than avail myself of them, I shall confess that the cause of these diseases is altogether unknown to me. It is certain that they do not owe their origin either to the imbibition of alcoholic liquors, or to eating any particular type of food, whether sour, sweet or bitter, whether of animal or vegetable nature." After a lapse of over 75 years substantially little can be added, aside from a mass of suggestive evidence which will be discussed seriatim.

1. Factor of Infection. The occurrence of sore throat, fever, joint pains, lymphadenopathy, and other such features, has led observers, with considerable justification, to the conclusion that erythema multiforme exsudativum is an infectious disease. However, numerous attempts to discover the precise causative agent have been fruitless, despite extensive bacteriologic investigations; cultures of blood have generally been sterile. In view of the clinical manifestations some have classed the affection in the category of focal infection, especially when the disease seemed to follow in the wake of a localized focus of infection (for example, fistula from a

tooth, etc.) [70]; others have assumed a streptococcal etiology on the basis of cursory analogies rather than of actual proof; and it has already been stated that there is little to commend a belief in the tuberculous hypothesis.

On the other hand, a mass of suggestive evidence, chiefly clinical in type, has been gathered in relation to the possibility of a virus infection. These data are based primarily on the association of the disease with lesions of the herpes group of affections. A host of observers have encountered an increased prevalence of erythema multiforme exsudativum during times when herpes zoster was particularly abundant.[55, 141, 142, 143] Lortat-Jacob [144] reported that the bullous fluid obtained from a typical case of hydroa vesiculeux gave a negative cornea test in rabbits. In one instance under my observation the patient showed, in addition to the eruption of erythema multiforme exsudativum, the lesions of both herpes labialis and herpes zoster of the left upper arm with an enlarged, slightly painful gland in the corresponding axilla. Bateman [6] was probably the first to note the concurrence of herpes iris and herpes labialis, while in recent years Forman and Whitwell [145] presented what seem to be cogent observations on the possible relation between these affections. In 12 consecutive instances of erythema multiforme (Hebra) they reported the clinical concomitance of herpes simplex or its occurrence just prior to the appearance of the former eruption. Moreover, they also noted that both diseases tend to recur, that in both sunlight may be a provoking factor, as will be noted later, and that both have a similar seasonal incidence. Considering, however, how common herpes labialis is and in view of a similar seasonal incidence, it is difficult to be certain that their simultaneous appearance in the same patient may not represent coincidence; yet, the number of cases in which Forman and Whitwell observed their concomitance would appear to be so great as to warrant serious consideration of this hypothesis, pending further investigation on the virus etiology. Urbach [146] recorded 20 cases in which herpes labialis preceded erythema exsudativum multiforme by a period of eight days; his experiments in animals, using blood and the contents of vesicles, gave negative results, but these observations seem to provide clinical substantiation of the data presented by Forman and Whitwell.

2. Factor of Food. What Hebra said regarding the failure to incriminate food as an etiologic agent in this disease would seem to apply today, though one possible exception will be mentioned shortly. Fordyce observed a case of herpes iris in the mouth, occurring after the eating of lobster; there was a subsequent recurrence, but it is not clear that this followed ingestion of the suspected food. A few isolated instances have been attributed to the intake of fish, oysters, etc., but the evidence presented is not very convincing. Morris and others were of the belief that beer was an occasional cause, and still others observed instances where the eruption was regarded as due to Bacchanalian excesses. It must be admitted, however, that the consumption of alcoholic beverages in various degrees is a practically universal custom,

and in the present state of our knowledge this factor can only be considered as a predisposing cause operating under circumstances that are still nebulous.

On the other hand, Bruce-Jones[147] has recently described a typical example of recurrent erythema multiforme exsudativum, presumably caused by the ingestion of caseinogen, and as this observation seems important, it merits a more detailed analysis. The reasons for Bruce-Jones' belief were: (1) a strongly positive intradermal reaction to this substance; (2) apparent reproduction of the disease following the *fifth* injection of caseinogen given in ascending doses for purposes of desensitization. Two subsequent attacks occurred after the ingestion of chocolate and ice cream, but it is not clear that the author intended to imply that caseinogen was the underlying factor in the production of these recurrences. This interesting observation needs the confirmation of additional such findings in other cases; attempts to reproduce recurrences in this disease ex juvantibus must be judged critically, and special care is required in eliminating the factor of spontaneous attacks of the disease due to the unknown agent causing the affection. The need to substantiate the above observation by the collateral method of skin-testing seems advisable. I have not seen an instance of this disease in which the etiology was clarified satisfactorily by means of skin tests, although it must be stated that no systematic efforts were made along these lines.

3. Factor of Sunlight. A few observers have recorded examples of erythema multiforme exsudativum in which the condition was apparently initiated by exposure to sun.[55, 148, 149, 150, 151] Ullmann[148] described a case featured by four recurrent attacks of the disease, each one following an intensive exposure to sunlight, and Klausner[149] reported three such instances. Kreibich[150] observed the simultaneous occurrence of erythema iris and erythema solare. These investigators were inclined to attribute a primary etiology to this factor. On the other hand, Polland[55] who cited an instance where the eruption was restricted to the parts exposed to light, believed that such exposure resulted in damage to the vessels, rendering them more susceptible to the unknown causal agent in the disease. Hübner[152] found evidence of an increase in the excretion of porphyrins in a group of 33 cases of erythema multiforme exsudativum; in eight patients there were observed findings that indicated to him probable damage to the liver. Thus far, definite substantiation of these observations is still lacking; moreover, the significance of such findings remains to be evaluated, as the entire subject of porphyrinuria is in a state of flux.

4. Multiple Etiology. There is a tendency to invoke the theory of multiple etiology whenever the cause of a disease is unknown, especially if it is one simulated by a host of other affections. Is it justifiable to consider erythema multiforme exsudativum as the counterpart of urticaria, one of the elementary reactions in the skin due to a variety of agents? The data recorded in this paper appear to indicate that this disease is a well-characterized entity in the sense of rheumatic fever as contrasted with " rheuma-

tism." In any event, before the concept of multiple etiology is permitted to gain sway, at least *one* cause should be definitely established, as in urticaria, and an effort must be made to distinguish between a predisposing factor (sunlight in herpes simplex) and the actual cause (virus in herpes simplex). In the present state of our knowledge it must be admitted that the etiologic factor or factors in erythema multiforme exsudativum remain to be discovered.

Treatment

In studying erythema multiforme exsudativum several principles illustrating rules in evaluating the results of therapy are exemplified. Owing to the essentially benign course of the average case of this disease, including those showing apparently severe constitutional symptoms, it is not astonishing that numerous remedies have received undue praise. The use of salicylates and related drugs, such as pyramidon and aspirin, is based on the belief in the rheumatic nature of erythema multiforme exsudativum, but the data recorded in a previous section are at variance with this hypothesis; favorable results appear to depend on their coincidental employment in mild cases. A healthy scepticism based on knowledge of the natural course of an affection and its variants should not be confounded with therapeutic nihilism, nor is an attempt at scientific evaluation of a drug inconsistent with its use for purposes of psychic treatment of a patient, especially if the differences between these attitudes are recognized. So far as the average example of this disease is concerned, there is more sophistry than logic in the statement that some cases are helped, others not; nor can undue significance be attached to an alleged shortening of the clinical course of individual examples, for variations in this particular are many and unpredictable. Nevertheless, experimentation with drugs is justifiable under circumstances to be defined shortly.

Among the drugs recently advocated in the treatment of this disease are germanin and sulphanilamide. In the section on prognosis it was stated that erythema multiforme exsudativum becomes a dangerous disease chiefly when the mucous membranes are affected, and it is in these cases that a more precise idea regarding the value of medication will be learned in respect to (1) the prevention of complications, such as bronchopneumonia and ocular lesions; (2) the shortening of the clinical course. It is, of course, understood that some attempt must be made to gain more accurate information relative to control cases of similar severity. The first essential, then, is to use the medication in those instances exemplifying a severe grade of disease. There is a fundamental objection against the employment of germanin in mild cases of the affection, for it is not an innocuous drug; sulphanilamide may be used, perhaps, with greater impunity, though the patient bears careful watching nonetheless. In all instances in which the oral mucous membrane is involved it is essential that careful attention be paid to the state of

the mouth, and in elderly persons the ordinary precautions against the supervention of hypostatic bronchopneumonia must be taken.

In summary, the treatment of erythema multiforme exsudativum is at present essentially symptomatic and empirical. In mild cases the use of dangerous drugs is to be deprecated; in severe examples, especially those featured by intense constitutional symptoms and involvement of the mucous membranes, there exists a definite field for the employment of such medication, but the precise evaluation of such therapy must remain for the future.

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A NEW OBSERVATION HELPFUL IN THE DIAGNOSIS OF CORONARY THROMBOSIS *

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The various descriptions of coronary thrombosis pain in the literature may be summarized as follows: The pain results from anoxemia of the cardiac musculature secondary to decreased blood supply; it is intense, unbearable, and amenable only to large doses of morphine; its location is usually under the lower sternum or in the epigastric region; the pain may be referred, among other locations, to the arms or jaw; the pain is continuous and is accompanied by varying degrees of shock.

In studying patients during attacks of coronary thrombosis, I have observed a pain syndrome which has not been mentioned or stressed in the literature on the subject.

The purpose of this article is to describe this syndrome. It has proved valuable in the diagnosis of obscure cases of coronary thrombosis, particularly in those patients in whom suspicions of this disease process could not be confirmed because of negative *early* electrocardiograms.

In evaluating substernal or epigastric pain which is possibly of coronary origin, it is important to consider carefully its quality. One must ask: Is the pain momentary or continuous? Is it periodic or rhythmical? Are its recurring intervals decreasing or increasing in number and in intensity of discomfort?

I have found the outstanding characteristic of pain in coronary thrombosis to be its rhythm and periodicity. This holds true for indefinite attacks and also for those in which the pain and shock are so prominent that the diagnosis is unquestioned. The pain comes and goes in cycles. It is unbearable for a variable short period of time and then subsides for a period equal to or many times longer than the actual pain. Then it returns again to be followed by another pain-lessened or pain-free interval. This cycle is usually repeated a number of times.

To establish the presence of periodic pains the patient must be observed closely for at least 15 minutes to half an hour, a longer or shorter period of time depending upon the intensity of the pain and on how soon after the beginning of the attack the patient is seen. Sometimes the return of pain is heralded only by increased restlessness, at other times by an anxious and painful expression accompanied by loud or subdued groans. These symptoms disappear with the return of the pain-lessened interval.

When the patient is first seen in an attack morphine should not be withheld. The administration of this drug will not obscure the diagnosis. If the above-mentioned pains are present, they will continue to recur and remain recognizable before the morphine exerts full effect.

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If the periodicity of these pains is observed, the diagnosis of coronary thrombosis can be made and will usually be substantiated by later positive evidence. This pain syndrome has proved invaluable in ruling out the presence of extracardiac anginas due to lesions above or below the diaphragm, such as acute gall-bladder disease, ruptured peptic ulcer, acute pancreatitis, intestinal obstruction, acute pneumothorax and pulmonary embolism or infarct.

The following charts describe various types of pain quality in coronary thrombosis. Each chart attempts to represent graphically the pain course in an actual patient who was observed in an attack. The cases chosen for analysis are typical of many other similar ones observed in various patients in ward, consultation, and private practice over a period of 15 years.

For comparative purpose, pain intensity is depicted as 0, 25 per cent, 50 per cent, 75 per cent, and 100 per cent. As there is no known accurate measure for pain intensity, these percentages are based on the patients' reactions, such as restlessness, groans, cries, facial expressions of agony, and general state of shock. Time intervals are spaced to represent the passing of five minutes. The letter P represents the time duration of pain. The height of P in relation to the rest of the chart depicts the intensity of the pain. The letter R represents relief and the duration of the relief. The amount of relief is depicted by the amount of fall from the pain level.

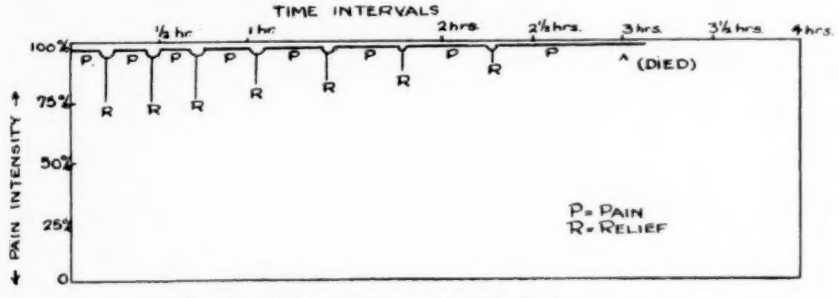

FIG. 1. Very severe attack with fatal outcome.

CASE REPORTS

Case 1. Male, 42 years old, was seized with sudden precordial pains. A diagnosis of "cold in the chest" was made by the first physician called. When seen by his own physician half an hour later, the patient's condition was diagnosed as coronary thrombosis. When examined by me, one hour and a half after the attack began, the patient was in shock, with the typical picture of acute coronary failure: profuse sweating, anxious pained expression, ashen skin, systolic blood pressure 0, pulse imperceptible. The diagnosis of this case was not confirmed by electrocardiograms or autopsy, but in view of a past history of angina pectoris and the subsequent findings, it is felt that the diagnosis was justifiable.

ANALYSIS

The chart shows the intensity of the pain in this patient to have been at the 100 per cent level. When first seen the pain paroxysms lasted about 10

minutes with the pain-lessened intervals of about five minutes. In the relief intervals the pain fell only to about the 75 per cent level. At the end of an hour it will be observed that the P intervals became longer and remained on the 100 per cent intensity level. On the other hand, the R intervals became shorter, descended less and less, so that even in the pain-lessened intervals the relief was not as marked as at the beginning of the attack. At the end of two hours (about three and a half hours after the onset) of observation the pain was practically continuous and the patient expired about one hour after the onset of this steady pain. One and one-half grains of morphine sulphate were given without any decrease in the intensity of the pain. This case is reviewed briefly to indicate that these pain and relief intervals are also present in unmistakable attacks.

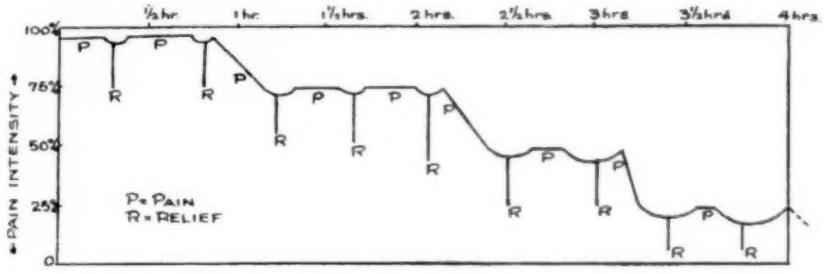

FIG. 2. Very severe attack with recovery.

Case 2. Male, aged 54 at time of attack in 1930. An electrocardiogram was taken at 2 p.m. due to a history suggestive of angina pectoris. Ten hours later, following heavy exertion, this patient suffered the severest attack of substernal pain, with recovery, that I have ever seen. He was pulseless, moribund, and terribly shocked; blood pressure was zero in the arm. A very slow pulse with many dropped beats first became palpable in about half an hour. His systolic blood pressure rose to 50 at the end of four hours. He remained in bed three months due to a complicating thrombophlebitis in each leg. He is alive today, probably due to the fact that the complicating phlebitis has greatly limited his activities. The electrocardiogram, taken 10 hours before his attack of coronary thrombosis, showed a prominent S-wave in Lead II. It was otherwise negative. After the attack the electrocardiograms showed typical changes in the S T intervals.

ANALYSIS

The intensity of the pain in the first hour was 100 per cent. It fell to 75 per cent in the second hour, 50 per cent in the third hour, 25 per cent in the fourth, from which point the pain gradually cleared up. In the first two and a half hours the pain paroxysms lasted 15 to 25 minutes, after which time they varied between five and 10 minutes, and disappeared at the beginning of the fourth hour to be replaced by a low grade aching sensation under the sternum.

The periods of relief, which lasted eight to 10 minutes in the first two hours, widened out to 15 and 25 minutes in the next two hours. The depth

of the relief periods increased progressively so that relief to the 75 per cent level of pain intensity in the first hour became almost complete relief in the fourth hour.

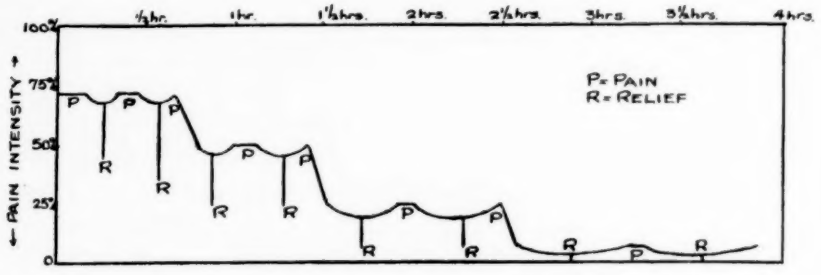

FIG. 3. Moderately severe attack with recovery.

Case 3. Forty-year-old male with no past history of discomfort. Pain was confined to the epigastrium; there was some vomiting; and at the time there was a question of gall-bladder disease. The patient was treated for coronary thrombosis because of recurrent pains and drop in blood pressure, and was in bed about six weeks. Recovery was uneventful, until sudden death about six months later after climbing five flights of stairs following a heavy meal. Coronary thrombosis in this case was proved by positive electrocardiographic findings.

ANALYSIS

In this patient the pain level was at the 75 per cent mark. He was not greatly shocked. The pain paroxysms were short, the relief intervals became quite long after one hour and a half, and the patient went on to recovery from the immediate attack.

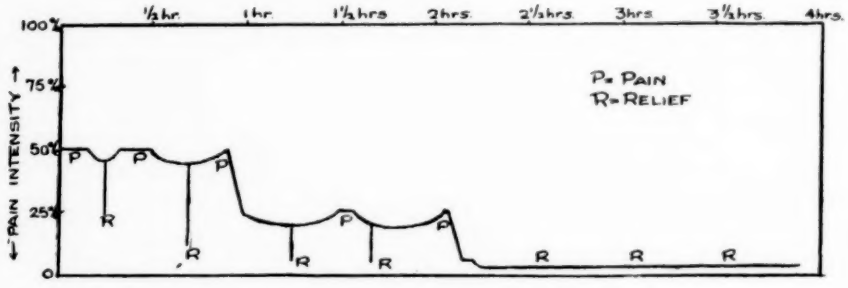

FIG. 4. Moderate attack with recovery.

Case 4. Male, aged 51. There was a history of substernal attacks of oppression on exertion for a number of months, and also of dyspnea and tiredness. The patient was seized suddenly with substernal discomfort while in bed at night. Coronary thrombosis was proved by electrocardiographic evidence and such clinical findings as fever, leukocytosis, increased sedimentation rate, and pericardial friction rub. The patient has had no recurrences, no evidence of congestive failure, and very few attacks of angina pectoris since his coronary thrombosis.

Analysis

This patient did not look very ill when first seen. His pain level was at the 50 per cent mark. Although his first attack of pain lasted 15 minutes, the relief interval lasted 10 minutes, during which time the pain disappeared entirely. The next pain paroxysm lasted five minutes, followed by freedom from pain which lasted 25 minutes. There followed two short pain paroxysms of lessened intensity. Relief set in at the one and one-half hour period, following which there was no pain recurrence.

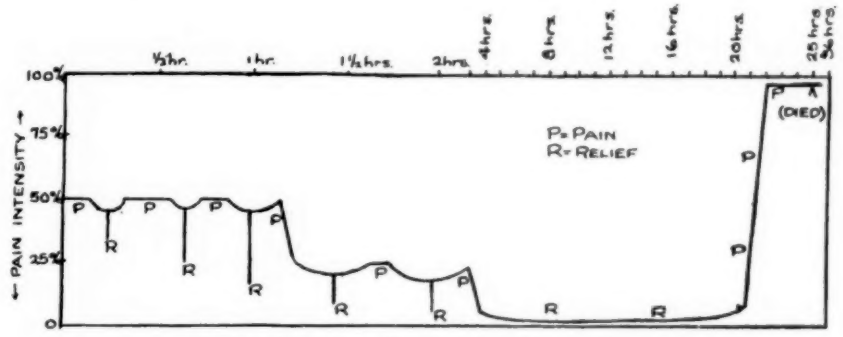

FIG. 5. Moderate attack with fatal outcome.

Case 5. Ninety-year-old male, who was three times a widower, and who had married a fourth time at the age of 82. He had been well except for occasional slight attacks of angina pectoris which did not prevent him from travelling and being quite active. His regular physician, who had seen him a few months before this attack, had made a diagnosis of arteriosclerotic heart disease—coronary sclerosis—angina pectoris—normal rhythm—Class 11A.

I was called to see this patient for the first time about half an hour after the attack began. It was a moderate attack. He did well until the next day when severe substernal pain returned and continued until death, 36 hours after the beginning of the attack.

The patient's own physician refused to concur in the diagnosis, which had been made only on the basis of the periodic pains suffered by the patient at the beginning of the attack. This physician diagnosed the condition as acute pneumothorax. Despite good heart sounds, normal blood pressure, and negative electrocardiographic findings (taken 30 hours after the onset), the diagnosis of coronary thrombosis was adhered to. An electrocardiogram taken half an hour before death (six hours after the first tracing) showed positive changes indicative of coronary thrombosis.

This case is enlightening, as it proves the value of correctly interpreting rhythmical pains when considering the possibility of coronary thrombosis.

Analysis

The pain remained at the 50 per cent level for the first hour. Each period of relief became deeper and longer. During the second hour the pain remained at the 25 per cent level, and the paroxysms lasted only five minutes. From the fourth hour to the twenty-second hour (observations of the nurses) there was complete relief from pain except for slight sub-

sternal ache. In the twenty-second hour there was a sudden sharp rise in pain from 5 per cent to 100 per cent intensity. It remained at this high level, little influenced by morphine, until the thirty-sixth hour, at which time the patient expired.

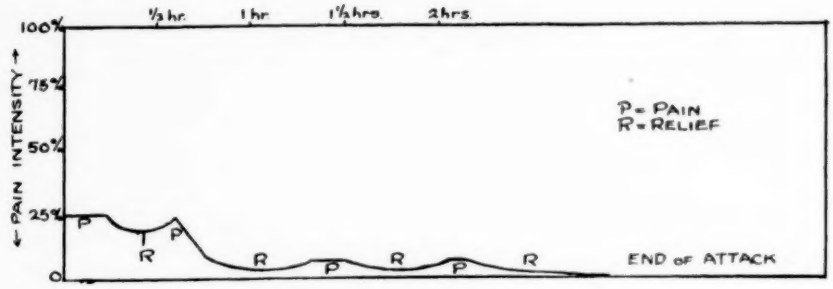

FIG. 6. Atypical attack with recovery.

Case 6. Male, aged 60. There was no history of angina. The patient complained of sudden epigastric discomfort following a heavy dinner, and of nausea, without vomiting. This discomfort produced a sense of 'being full of gas' rather than of having pain. The patient was greatly relieved after belching. There had been four paroxysms of this discomfort, on the basis of which a diagnosis of coronary thrombosis was made and proved by electrocardiograms. The patient remained in bed four weeks after finally being convinced that he was not suffering from indigestion. He made an uneventful recovery.

ANALYSIS

The intensity of the pain was at the 25 per cent level. There were two paroxysms in the first hour, lasting respectively 15 and 12 minutes. In the second hour the paroxysms lasted 10 and 5 minutes, and were on a 5 to 10 per cent intensity level. Complete relief came at the end of two and one-half hours.

COMMENT

The six cases chosen as examples typifying rhythmical pain run the gamut from very mild to most severe attacks. A study of a large series of cases will present variations as numerous as the cases themselves. In some the rhythmical sequences of pain and relief are absolutely regular for a few hours; in others there is no regularity. The intensity and length of the pain paroxysms may be increased suddenly following a preceding decrease. The recurrent pain episodes are sometimes unrecognizable in those very severe attacks in which the patient is prostrated. The pain syndrome which has been described will be recognized in most cases of coronary thrombosis if the physician takes the time and pains to observe his patient closely and continually. It must be emphasized, however, that absence of this syndrome should not make for a negative diagnosis in the presence of other positive findings. Early negative electrocardiograms in questionable cases

should not influence the physician against a diagnosis of coronary thrombosis if he has observed at least three recurrent pain paroxysms. The patient should not be discharged as being free from this disease unless serial electrocardiograms are negative and other evidence is lacking.

The cause for the recurring pains is difficult to prove. Theoretically, it might be explained on the basis of the changing level of anoxemia which is dependent on the adjustments which the cardiac circulation is called on to make in the first few hours following the immediate shock of the attack.

The pain of an attack of coronary thrombosis may be compared with the pain of a number of successive attacks of angina pectoris which follow one another closely. The pain and rest intervals in coronary thrombosis differ from these only in that the pains are more severe in the former and are unrelated to exertion. When viewed in the light of the similar underlying pathology of the two conditions it seems natural to compare the pains of the coronary thrombosis patient who is resting with those of the angina patient who is exerting himself. Both conditions are usually the result of an underlying coronary sclerosis, and each could well be listed under the heading of acute coronary failure.

In attempting to describe the rhythmical pains of coronary thrombosis I have referred to them as labor pains of the heart. This comparison has been employed after due consideration, because no other type of rhythmical pain in medicine is as commonly known to every physician as the physiological labor pains of the woman at term. The similarity between these pains and those of coronary thrombosis is often striking, and of great prognostic value. That patient usually succumbs who has periodic substernal or epigastric pains, which resemble the uterine pains of the pregnant woman just before delivery. Here the bouts of pain become longer and the rest intervals shorter, until such time as there is no pain-free interval. If, however, the cardiac pains resemble those of uterine inertia, i.e., strong at first but gradually becoming weaker and farther apart, until they stop, the patient usually recovers from the immediate attack.

Summary and Conclusions

1. Descriptions of coronary thrombosis pain in the literature do not mention or stress the importance of evaluating the quality of this pain.

2. The outstanding characteristic of this pain is its rhythm and periodicity.

3. The patient must be observed carefully before the presence of these characteristics can be determined.

4. If the periodicity of these pains is observed, the diagnosis can be made and will be substantiated by later positive evidence.

5. An analysis of six patients has been made to describe this pain syndrome.

LIVING WITH THE WEATHER*

By F. M. Pottenger, M.D., F.A.C.P., *Monrovia, California*

Shift from Bacteriologic to Physiologic Interest in Medicine

When bacteriology supplied the cause of infectious diseases it gave definite direction to the development of medicine, both preventive and curative, for several decades. By learning the cause and the method of transmission, preventive measures were instituted more or less simultaneously throughout the world. The effects of these were shown everywhere by a reduction in morbidity and mortality. As a result, in the United States the general death rate dropped from about 18 per 1,000 of the population 50 years ago, to about 11 today. Since most of the preventive measures have been particularly operative in case of diseases which affect the young, those who formerly would have died during the first two or three decades of life now live on to mature years or even old age.

Whereas 50 years ago about 95 per cent of illness was acute, today 75 per cent of it is chronic. This shift in the nature of illness has changed medical thought and practice; and physicians are now devoting more of their study to problems of development, the chronic infections, degenerative and deficiency diseases, and to disturbances of a functional nature.

The change in type of disease calls for a more intensive study of the patient; and physiology now becomes of greater importance than bacteriology in providing an understanding of present-day medical problems. As physiologic knowledge increases, its contribution to the understanding of all diseases becomes more and more important. Even defense against infections is a physiologic process; and the scientific treatment of all diseases follows physiologic principles.

In our study of man as a physiologic being we are impressed with the fact that he is influenced by many stimuli of both a physical and psychic nature. They may originate either outside the body or within. Internal stimuli may be set free by such processes as the digestion of food within the gastrointestinal tract; by parenteral digestion of proteins; by secretions of various kinds; by bacterial toxins, or other toxic substances which arise within the body; or, by stimuli of emotional origin. Stimuli which arise in the external environment are also of many types. Among those which most frequently cause helpful stimulation, on the one hand, or stresses and strains which unbalance the physiologic mechanism, on the other hand, are the atmospheric forces in the midst of which we live, but to which we fail to assign a position of importance.

* Read at the Twenty-third Annual Clinical Session of the American College of Physicians, New Orleans, March 30, 1939.

Man's Physiologic Adaptation to Meteorologic Forces

The human body is a receptor mechanism which receives and transforms stimuli of various kinds and varied intensity into action. It has a remarkable power of adaptation. One who is physiologically stable has the ability to adjust to heat equal to that in the tropics and to cold equal to that in the Arctic; to an atmosphere saturated or one almost devoid of moisture; to a gentle zephyr or to a wind movement of hurricane proportions; to a low or high barometric pressure; to light of great or of little intensity; and to varying degrees of electric potential.

Atmospheric forces are rhythmic in nature, varying daily, seasonally, and cyclically. They also vary geographically. The forces may be mild or turbulent. The varying reactions with which man responds may depend on constitutional or acquired differences. He varies in reaction in illness and in health, and at different age periods. He may possess organs with varying susceptibility. Some men might be particularly subject to diseases of the respiratory tract; others to diseases of the cardiovascular, renal, gastrointestinal, endocrine or blood systems. From this it can be seen that there are many variables which will determine or modify the manner in which man's physiologic mechanism will react to the atmospheric forces; and it is evident that he does not adapt so readily or so completely when ill as when well.

There is a difference in opinion as to what particular atmospheric force is most potent in causing changes in the body's reaction. It may be, as far as present knowledge is able to determine, some one or some combination of several forces. The action of any force which produces stimulation is shown in changes in oxidation. This may be confined locally or expressed widely. The stress falls heaviest upon tissues which are the seat of pathologic change because the cells which are involved have altered reactivity. A hyperactive cell has its electric reactivity altered and its permeability increased. So, strong stimuli may produce effects which are purely physiologic, or effects which fall outside of normal physiologic limits and result in dysfunction or disease. If disease is already present in a quiescent state, they may reactivate it. They may increase activity if the process is already active, or they may even cause death of the patient.

The usual effects of atmospheric forces of normal intensity impinging upon the body of the average man in health fall within the point of normal physiologic stimulation. However, at times of storm the stress is multiplied many times and may produce harmful effects. Thus we live and enjoy, become ill, improve or fail to improve and die with the weather.

If we attempt to explain how these effects are produced, we will find difficulty in establishing the cause with absolute definiteness. However, careful observation of groups of people will make it possible for the observer to satisfy himself beyond doubt that people in general are meteorologically influenced in their reactions, and that different individuals react with different degrees of intensity to the same stimulus.

Physiologic Effects of Different Meteorologic Forces

Some of the earliest studies in this country were those of Huntington.[1] He stressed the effects of temperature and humidity. He made a study of the daily work of three or four thousand mill operatives in New England, and the Southern States, also of 1700 students at Annapolis and West Point. He found that the daily variation of temperature in which the mean maximum was about 64° F. and the mean minimum was about 38° F. was the most favorable for productive effort. Of course, humidity, wind movement and other forces are modifying factors. Another important factor was the changeableness from day to day. He found that neither too great changes

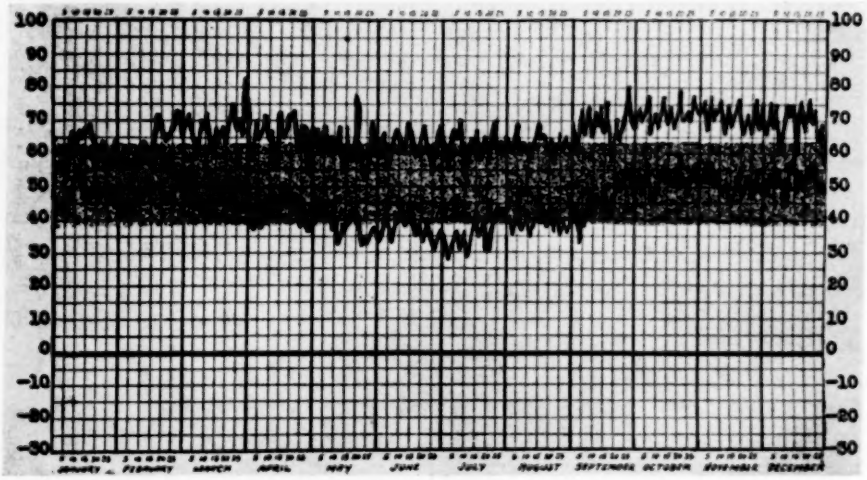

Fig. 1. Daily maximum and minimum temperatures, Sucre, Bolivia, 1923 (Mills).

nor monotony were favorable for best physical or mental accomplishment, but that moderate variability added to climatic efficiency. He called attention to the fact that in the past, atmospheric features similar to those which he described as optimal were present at the time that many nations reached the pinnacle of their civilization.

Petersen,[2] in his epoch-making observations, has studied the effects of the various meteorologic forces upon the many physiologic reactions of normal men with different constitutional peculiarities, as well as those suffering from different diseases.

Likewise he has endeavored to determine the force which affects man most and stresses particularly barometric change which is most marked at times of storm.

Mills [3, 4] has studied the demands made by daily variations in temperature on people living in different climates. He has particularly noted the effects according to the manner in which they depart from the optimum temperature variation established by Huntington. This he illustrates by the following charts. In each figure the stippled band represents Huntington's optimum

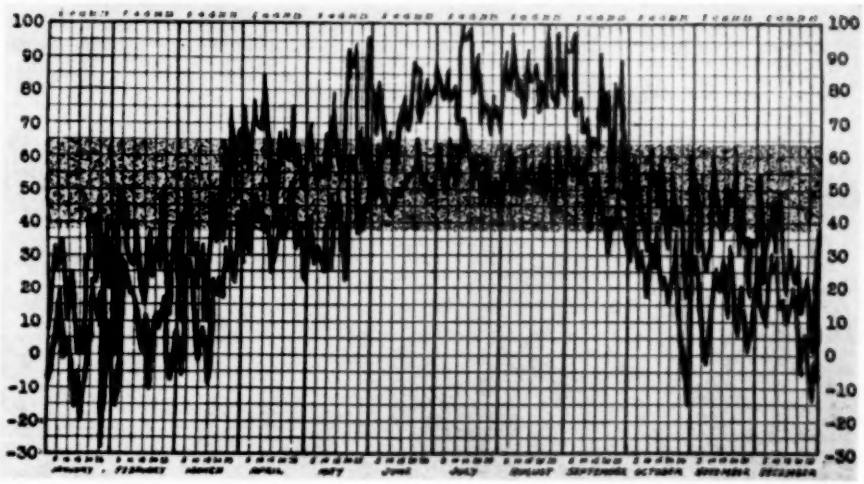

FIG. 2. Daily maximum and minimum temperatures, Bismarck, North Dakota, 1925 (Mills).

daily variation. Figure 1 represents a climate in which the diurnal variation in temperature for most of the year falls within this optimum, hence is a climate which favors productive effort throughout the year. Figure 2 is one in which both daily and seasonal variations show wide swings calling upon the individual to make enormous daily and seasonal compensation. Such a climate is rigorous and calls for adaptation which the less vigorous may not be able to make. Figure 3 is a monotonous climate such as is found in the tropics where the temperatures, both daily and seasonal, fall outside and above the optimal limits.

Under conditions of optimal temperature man is able to accomplish most,

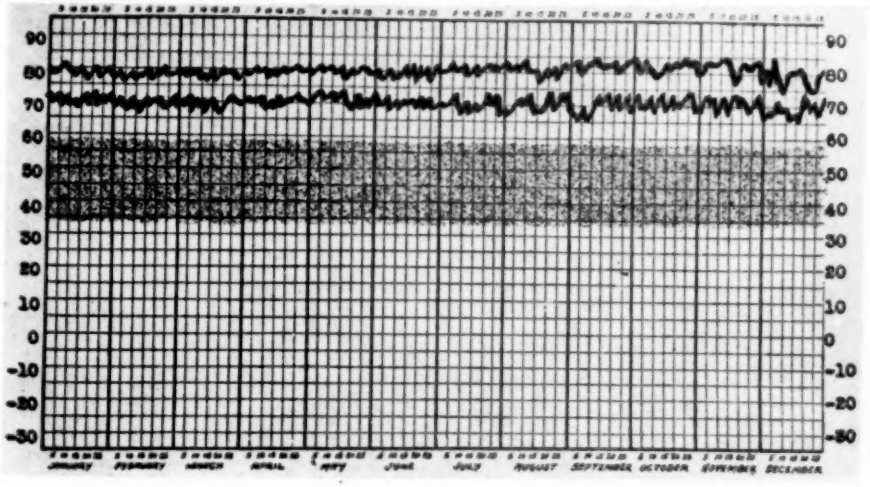

FIG. 3. Daily maximum and minimum temperatures, Georgetown, British Guiana, 1923 (Mills).

and is best able to maintain health. The temperature with great daily and seasonal variations makes extraordinary demands upon man's adaptive mechanism, and may precipitate disease in those with low resistance. On the other hand, it stimulates the strong to withstand unusual effort and raises their resistance to disease. Those who live in monotonous non-stimulating climates do not suffer from diseases which are produced by stress, such as hypertension, hyperthyroidism and diabetes, to the same extent as those who live in more rigorous climates.

That the prevailing diseases from which people suffer in these various climates would differ is to be expected. So is it reasonable that the same disease might affect people of these varying climates differently. It is well known that the people of the tropics do not show the same resistance to tuberculosis that is shown by those who live in the temperate zone, also that the less resistant patients do not withstand the rigors of Northern winters as well as those who are more vigorous.

Appendicitis is more common in the more stormy portions of the United States than in the warmer, milder portions, but the mortality is greater in the latter probably because of the lack of the invigorating meteorologic forces which increase the patient's ability to withstand.

The rigors of the North increase the incidence of such metabolic disorders as thyroid disease, diabetes and pernicious anemia, as shown by Petersen and Mills.

Storms

All atmospheric forces are more turbulent at time of storms, and physiologic mechanisms are called upon to make greater compensation. Storms, in the meaning here used, denote the condition in which the air, warmed in the tropics, is sent Northward producing a high pressure area which meets the cold air from the Arctic regions coursing Southward, thereby producing a low pressure area. The struggle between these air masses is productive of a turbulence which is designated as a storm. The barometric pressure changes; temperature and humidity are altered; air currents vary, and electric potential shifts.

The major factors which determine the direction and course of these air masses are the masses of water and land, and the contour of the land, as modified by mountains, river valleys and plains. These being fixed and definite, the storm tracks are accordingly quite definite. The paths for the storms on the American continent descend from the North Pacific through the Mackenzie Basin or from Alberta and enter the Northwestern part of the United States, then they course Southward along the Eastern slope of the Rockies until they are deflected Eastward and Northward to pass over the Great Lake region and down the St. Lawrence Valley. Many of them pass farther Southward over the Mississippi Valley, but the main tracks keep well to the North. The Great Lake region has the reputation of being the stormiest area in the world. Northern Europe, on account of the land

and water topography, escapes much of the storminess which dominates the Northern part of the United States. Excessive storminess is accountable for the rigorous, variable climate in the Northern portion of the United States, and calls for a hardy people.

If one would comprehend the possible sum total of effects produced on man by atmospheric forces, he must consider both the daily and cyclical changes which occur in air masses; and that all differences in temperature, humidity, velocity, changes in ionization and electric potential, and differences in light transmissibility require adjustment. Think of the adaptation that is required of man to adjust to air movement when it attains a velocity of cyclone proportions, or of the rapid changes in barometric pressure at the time of tropical storms!

How Atmospheric Forces Produce Effects

These atmospheric forces produce their effects through all of the physiologic mechanisms of the body, nerves, hormones and body electrolytes. They act primarily upon the skin with its rich supply of sensory nerves. These transfer the stimuli centralward where they are transferred to motor mechanisms, usually of the vegetative system, to be distributed to the various parts of the body for action. Some of these forces, too, produce psychic effects which may result in either normal or pathologic stimulation of the physiologic mechanisms.

The fact that the stimuli act upon all of the physiologic mechanisms is illustrated by the effects of heat stroke in which the loss of sodium, the deficiency of the adrenals, and reduced sympathetic stimulation each make up a part of the picture.

Meteorologic forces may bring about general physiologic response or a response limited to some particular organ. The latter may be the case when the organ is the seat of disease which prevents full and free physiologic adaptation.

There is nothing specific in these meteorologic forces. They produce effects similar to those caused by other stimuli which produce general physiologic effects. This may be illustrated by pulmonary and pleural pain. Patients who have had pulmonary tuberculosis with involvement of the pleura may, long after the disease ceases to be active, suffer from pains in those sensory nerves which were reflexly influenced at the time of the acuteness of the process. Such pain is frequently brought on at the time of storms. However, it may come with other forces which act widely upon the physiologic mechanism such as emotional stress, infections, tiring, and menstruation. The same is true of other types of visceral pain. It has long been recognized that the arthritic is sensitive to weather change.

These general physiologic stimuli are by no means always harmful. Mild meteorologic effects produce normal body activity and aid in restoring health when damaged. This is shown in the effects of favorable climatic influences and pleasing emotions upon people.

Effect of Meteorologic Forces on Disease

Ill effects, too, may be shown in observing the clinical course of a disease, such as tuberculosis. Hemoptysis, pain, insomnia, pleural effusion, metastatic spread, and exacerbations appear seasonally; and also appear in multiples at the same season, being precipitated by storms. The season which shows most exacerbations and most spread of the disease is the late winter and early spring, after the patient has been long subjected to the stresses of winter weather. A period of lesser severity is shown in the fall at the approach of winter.

There is five or six times as much acute miliary tuberculosis in the spring as there is in midsummer. The same is true of tuberculous meningitis among children. This is shown in figure 4, from Engel and von Pirquet.

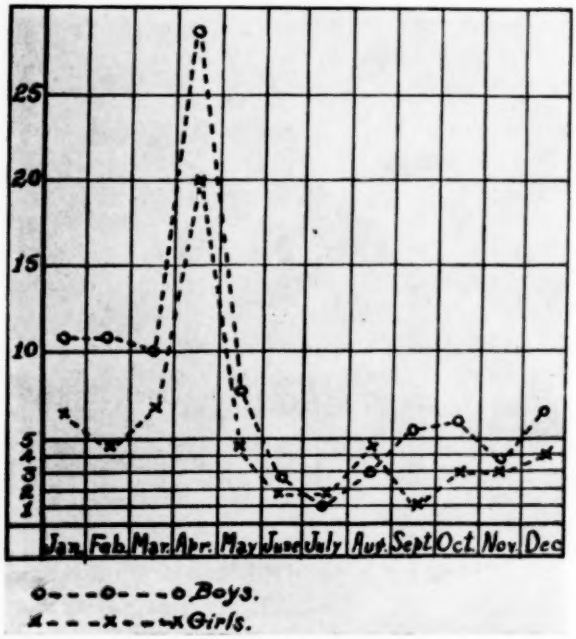

Fig. 4. The relative percentage of cases of tuberculous meningitis in children for the different months of the year, showing the enormous increase in the spring months and low percentage in summer (Engel and Pirquet: *Handbuch der Kindertuberkulose,* 1930, i, 531).

For many years we have observed that there is a seasonal increase in the number of severe cases of tuberculosis at the end of winter and early spring. Moreover, we have noticed that storms hasten death in patients who are quite ill.

Figure 5, from the 1937 Health Report for the City of Sheffield, England, shows numerous curves, but I wish to call particular attention to the atmospheric temperature curve; the death rate from all diseases, that from heart disease, and tuberculosis and other respiratory infections. It will be

noted that the preponderant number of deaths occur in the colder months. These are not only the months of storm, but the months in which the effects of storms are cumulative, so that after a succession of severe stimulations the patient's resistance is lowered and easily overcome. The death rates in many of our large Northern cities have been analyzed by Huntington, Peter-

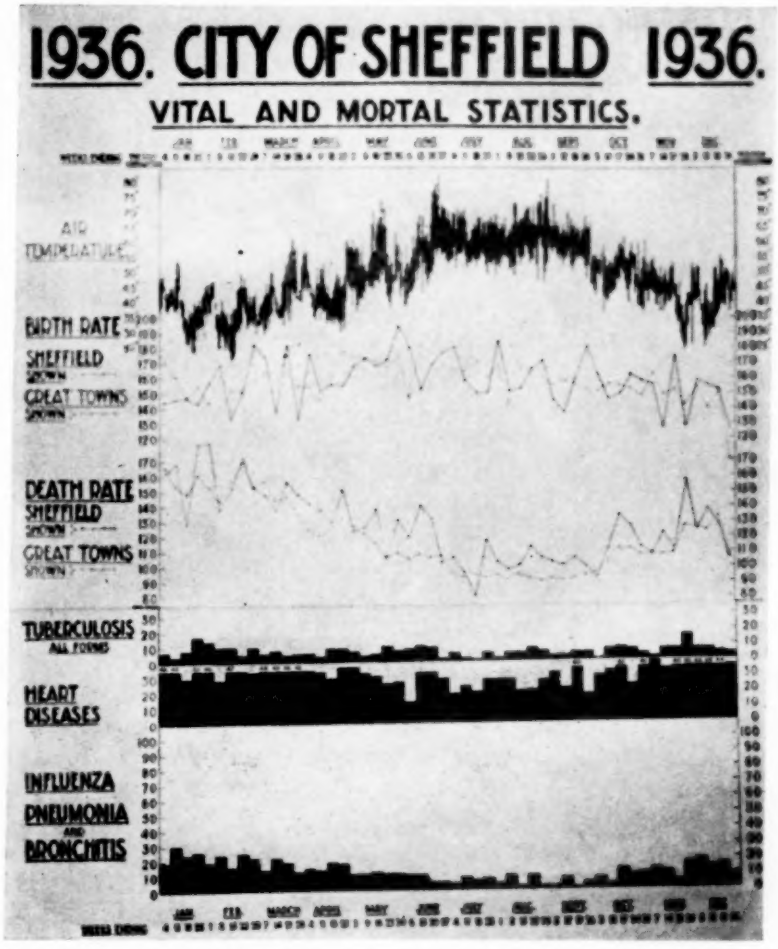

FIG. 5. The relation of mortality curves to temperature and seasons. (Annual Report on the Health of the City of Sheffield for 1936.)

sen and Mills, and show the same increase in the cold and stormy winter and spring months.

Figure 6 shows the temperature chart of five patients who were in the sanatorium at Monrovia during April and May of 1938. Their temperatures are plotted against the barometric, temperature and humidity records of the period. It will be noted that on April 22 and 23 the temperature and humidity increased, preceding a slight drop in the barometer, and that four

of the patients show slight clinical disturbance. The most marked atmospheric changes came on May 4 and 5, when there was a drop in the barometer, and elevation of temperature and a continuation of a high humidity which was preceded by a rain on the first and second of the month.

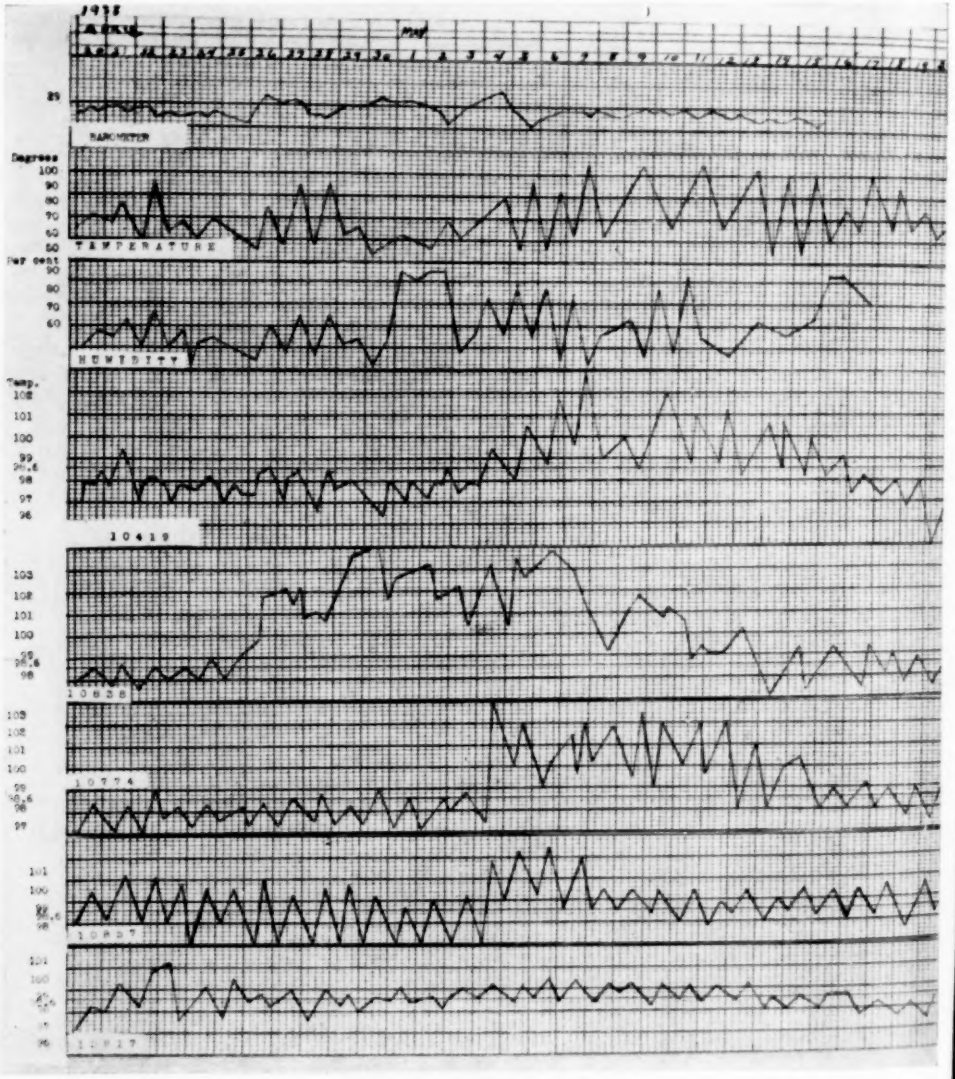

FIG. 6. Relation of symptoms and complications in tuberculous patients to meteorologic factors.

It will be noted that patient 10419 showed the beginning of an active tuberculous process which lasted two weeks. Patient 10838 was suffering from a complicating pleurisy with effusion. The temperature had attained a maximum and was receding, but showed the beginning of a second eleva-

tion on the fourth. Patient 10774 had been free from temperature or complications for months and developed a pleurisy with effusion which began on the fourth. Patient 10857 was a psychoneurotic who was recovering from a streptococcal infection. Note the sensitiveness to meteorologic forces as shown in the temperature elevation on the same day as the others. Patient 10817 showed a smaller elevation of temperature on the fourth than she did on the 21 and 22 of April, but it was accompanied by a mild activity in her pulmonary lesion.

In observing many patients over the past 35 years, we have noted that exacerbations of the tuberculosis and complicating lesions, such as pleurisy and hemoptysis, are atmospherically conditioned and are especially connected with storms.

Nor is the seasonal influence confined to human beings and their diseases. Brown [5] reports that there is an increase in the incidence and in the metastatic rate shown by mice infected with syphilis and with experimental malignancy in the late winter and early spring, and further that this harmonizes with the seasonal variation in organ size and weight.

Just what force or forces are responsible for these effects is not clear. In Southern California, where changes in barometric pressure are slight, we note the same phenomena that are noted in more rigorous climates where the fluctuations are greater. It may not be the barometric pressure or the changes in temperature which are responsible, but a combination of several or all atmospheric forces. In this connection a most interesting observation is reported by the Russian physicians who are studying man's reaction to the weather in connection with the attempt to plant colonies in the Arctic regions. They have found that two or three days before the approach of a violent Arctic winter storm the contractions of the heart decrease, sometimes to about half the normal number per minute, and that the output per contraction increases in proportion. Moreover, this occurs two or three days before any meteorologic instruments register any warning of approaching change.

Body chemistry, endocrine function and the sensitivity of the components of the vegetative system all show seasonal adaptations. In the winter the tissues are more active, cells more permeable, and the potassium is more prominent than calcium. In the summer the reverse is true. It readily can be understood that there should be a difference in the incidence of those diseases which are seasonally conditioned. It can also be surmised that there would be a difference in diseases which are conditioned by atmospheric forces.

Man is a constitutional and developmental variable, possessed of individual powers of reaction under conditions of both health and disease. He lives in an atmosphere disturbed by many forces, which are subject to diurnal, seasonal and cyclical changes. These various forces react upon his physiologic mechanism and cause many changes in its efficiency, sometimes calling out favorable response, again producing harmful effects. These

reactions may result in well-being and conditions of health; in conditions of malfunction and disease; and eventually in healing with restoration to health; or in death.

Man lives happily, he becomes ill, and recovers or dies with the weather.

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CASE REPORTS

RECOVERY FROM ACUTE FRIEDLÄNDER PNEUMONIA; REPORT OF A CASE AND REVIEW OF LITERATURE *

By MILTON M. HARTMAN, M.D., *San Francisco, California*

ACUTE primary Friedländer bacillus pneumonia is such an uncommon and highly fatal disease that any recovery from it should be reported in the hope that our present therapeutic armamentarium may receive some useful modification or addition. When the patient surviving this usually fatal type of infection is 70 years old at the time of his illness, thereby becoming the oldest reported case, his physician has the additional pleasure and privilege of reporting a medical curiosity.

As shown by Sisson,[1] Belk,[2] and Solomon,[3] primary Friedländer bacillus pneumonia presents a definite clinical picture, with a characteristic age incidence (the large majority of cases occur in the fifth and sixth decades of life), peculiar sex distribution (about six times more frequent in males), high toxicity, characteristic sputum (markedly sticky and stringy), and a high mortality. In smears of sputum the fat encapsulated Gram-negative rods, varying in length from 0.5 to 5 microns, are striking. Unmistakable are the cultural characteristics, particularly the "nail-head" appearance in gelatin stabs, and the raised, gray, sticky, mucoid colonies on agar plates. As with the pneumococcus, there are biological differences within the species. In 1926 Julianelle,[4] by the study of agglutination and precipitin reactions, was able to distinguish three types: A (by far the most frequent), B, and C, comprising most of the clinically important strains. All other strains fell into a heterogenous group X. This group X will no doubt undergo the same dismemberment that the pneumococcus group IV underwent. The Friedländer bacillus, known also as the pneumobacillus, *Bacterium pneumoniae, Bacillus mucosus-capsulatus,* and *Klebsiella pneumoniae,* is found present in the upper respiratory tract of a small percentage of normal people. Incidences of ½ to 8 per cent have been reported. Bloomfield [5] found it in 5.8 per cent of normal people, most frequently localized in the tonsils.

The bacteriology, pathology and clinical course of primary Friedländer pneumonia have been reported in detail: we now know a good deal about the fatal cases. We do not know with any accuracy, however, the actual incidence of the disease, what clinical factors lead to recovery, and what therapy, if any, has been found effective. The author, therefore, has made as complete a search as possible of the literature from 1882 to 1937 inclusive, with particular reference to the incidence of acute primary Friedländer bacillus pneumonia as compared to that of acute pneumonias as a whole, the number of reported cases, the number of reported recoveries, and the details of treatment in the latter group. The task was complicated by the fact that when Carl Friedländer [6] described the dis-

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From The Department of Medicine, Stanford University Medical School. Approved for publication by Dr. A. L. Bloomfield.

ease and the etiologic agent in 1882 he dealt mainly with necropsy material in which the bacillus in question was a secondary invader. He believed that it was the chief etiological agent in lobar pneumonia. In the next few years the work of Sternberg, Frankel, and Talomon in studying the pneumococcus led them to believe that the Friedländer bacillus was never the primary cause of pneumonia. It was Weichselbaum,[7] in 1886, who first stated the truth of the situation, that the Friedländer bacillus is the primary etiological agent in a small but definite percentage of cases. Howard [8] agreed, but set the incidence at 5 per cent. The result of the conflict in opinions of these early investigators, coupled with errors in bacteriological technic and classification of organisms and changing nomenclatures, was that early statistics on the bacteriology of respiratory diseases and the bacteriological data on most case reports were worth very little. Not until about 1905 were bacteriological technic and classification so standardized that statistics commenced to have real significance.

Incidence Relative to All Primary Pneumonias

In attempting to get a true idea of the percentage of pneumonias due primarily to the Friedländer bacillus in recent years one finds only four series suitable for analysis. These four are: (*a*) the only ones large enough to be statistically significant; (*b*) reported by men of unquestioned ability; (*c*) reported from records of hospitals whose diagnostic and laboratory standards are preeminent. Curiously enough all of the aforementioned cases are from New York or its vicinity. The incidences in the individual series are 0.4 per cent, 0.62 per cent, 0.64 per cent, and 1.08 per cent. In the total number of 11,248 pneumonias 86 cases of primary Friedländer pneumonia were found, a relative incidence of 0.76 per cent.

Table I

Author	Locality	Year Reported	Years Covered in Survey	Total Number of Pneumonias	Number of Friedländer Pneumonias	% of Friedländer Pneumonias
Avery [9] Chickering Cole Dochez Cecil [10]	Rockefeller Institute	1917	Not Stated	480	3	0.62%
Baldwin Larsen	New York	1927	Not Stated	2,000	8	0.4%
Solomon [3]	Bellevue Hosp. N. Y.	1937	1920–1937	5,000	32	0.64%
Bullowa [11]	Haarlem Hosp. N. Y.	1937	1929–1936	3,768	41	1.08%
			Total	11,248	86	0.76%

There were several large pneumonia series reported from Europe, but these lacked specific data on Friedländer bacillus infections. Once the pneumococcus was excluded as the etiologic agent the investigation of the remaining cases was not pursued by the laboratories, either because of lack of interest or finances. The above figure, 0.76 per cent of all pneumonias, is as accurate as the available data allow. A few investigators have reported a higher incidence based on

small series of pneumonias, whereas others have reported an extremely low incidence. Interesting extremes are those of Bhatnagar and Singh,[12] who found 13 cases in 100 consecutive pneumonias in India, and of Baehr, Schwartzmann and Greenspan,[13] who found only two cases in the last 36 years at the Mount Sinai Hospital, New York (a hospital of 856 beds having 14,749 admissions in 1936).

Reported Cases

In 1915 Sisson[1] completely reviewed the literature on primary Friedländer bacillus pneumonia to that date. Because of the previously mentioned unsettled status of bacteriological technic and classification and the early pneumobacillus-pneumococcus controversy, he was forced to conclude that up to that time only 33 cases had been so fully studied and reported that they could be considered pneumonias due primarily and solely to the Friedländer bacillus. These included only two recorded recoveries, a case of Chirie in 1906 and one of Pic and Durand in 1914. He mentioned that Apelt and Phillippi each had had one recovery, but neither of these cases was mentioned or reported in journals by the authors themselves; their reported cases were all fatalities. Sisson also mentioned Stuhlern's three recoveries in a series of 10 cases in 1904, but he strongly doubted (as does the author) that Stuhlern was dealing with the Friedländer bacillus. Sisson reported four cases of his own, including one recovery. The situation, then, in 1915, was 37 recorded cases with three recorded recoveries.

The author was able to discover in the more voluminous and more accurate literature since Sisson's day an additional 247 cases, in both case reports and in mere mention in various pneumonia series. In 196 cases (80 per cent) complete clinical records or satisfactory summaries were obtained, either in journals or personal communications from hospital staffs and living authors. The 51 remaining cases were reported from reliable institutions but no further information was obtainable except that they had occurred. The mortality in this latter group is pure speculation; presumably all cases died.

Recorded Fatalities and Recoveries from Friedländer Pneumonia

Table II

Sisson 1882–1915	34 fatalities	3 recoveries
Hartman 1915–1937	185 fatalities	11 recoveries
Totals	219 fatalities	14 recoveries
	Fatalities plus recoveries 233	
	Mortality 94 per cent	

It was interesting to find that only five cases had been reported in children: Etienne[14] reported one in 1895, Comba[15] one in 1896, Ferguson and Tower[16] two in 1933, and C. H. Smith at the Bellevue Hospital, New York, one in 1937. In 1916 Zander[17] described an epidemic of what he thought was acute primary Friedländer bacillus pneumonia in a German labor camp. His report of 144 recoveries in a group of 411 cases was amazing. However, he performed no autopsies, and made no sputum smears or cultures and no serum agglutination tests, his diagnosis being made entirely on clinical evidence. His average age of 25 years and mortality rate of 35 per cent are entirely at variance with the experience of other investigators who have noted the high mortality and peak

incidence in the fifth and sixth decades of life. The relatively mild clinical course described and mortality rate are more in accordance with reports of other authors of influenzal pneumonia prevalent at that time in large groups of overworked and undernourished men.

Reported Recoveries from Primary Acute Friedländer Pneumonia

Only 14 recoveries, including the case of the author, are available for analysis. The significant clinical data are summarized in table 3. In addition to the specific treatment mentioned, all patients received the routine supportive and symptomatic pneumonia therapy of the time.

Table III

Author	Year Reported	Number of Recoveries	Age	Race	Sex	Days Ill	Leukocytosis	Blood Culture	Treatment and Remarks
Chirié [18]	1906	1	17	Wh.	F.	26	?	Pos.	Colloidal silver intravenously
Pic and Durand [19]	1914	1	43	Wh.	M.	22	Yes	Neg.?	Vaccine. Complicating pyopneumothorax drained
Sisson [1]	1915	1	31	Wh.	M.	70	Yes	Neg.	Complicating pyopneumothorax drained. Well month after
Abrami and Worms [20]	1930	1	23	Wh.	M.	13	Yes	Neg.	Trypflavine intravenously
Solomon (Bellevue Hosp.) [3]	1937	1	48	Wh.	M.	15	Yes	Neg.	Routine supportive treatment only
Bhatnagar and Singh [12]	1937	1	40	Wh.	M.	11	Yes	Neg.	Routine sup. treat. 1 : 1000 agglutination titre noted
Bullowa (Haarlem Hosp.) [11]	1937	7	36	Neg.	M.	7	Yes	Neg.	Routine sup. treat.
			57	Neg.	M.	10	Yes	Neg.	Routine sup. treat.
			41	Neg.	M.	11	Yes	Pos.	Routine sup. treat.
			26	Neg.	M.	7	Yes	Neg.	Type A serum
			28	Neg.	M.	6	Yes	Pos.	Type A serum
			36	Neg.	M.	8	Yes	Neg.	Type A serum
			52	Wh.	M.	12	No	Neg.	Type A serum
Hartman	1938	1	70	Wh.	M.	23	Yes	Neg.	Iodides to limit of tolerance. Sod. citrate to counteract acidosis. Digitalis, quinine and adrenalin as explained in history
Average Case Age			39						

Case Report

The patient, G. V. H., was a white male, aged 70, of Hungarian extraction.

Family History: Not significant.

Past History: For the past 25 years the patient had suffered from bronchial asthma and associated chronic bronchitis. These varied in severity, usually being exacerbated in the winter. Twenty years ago he had had a septum resection and bilateral inferior turbinectomy on the advice of his physician. He had been skin tested recently with the usual allergens and found negative. By elimination, he was diagnosed as a "bacterial asthma." His sputum had been examined six times in the last five years. No acid-fast bacilli were found. A mixed flora of streptococci, pneumococci, small Gram-negative bacilli, and occasional spirillae was present. Of

note in light of later events is the fact that the administration of iodides to the limit of tolerance never made any difference in the character of his sputum, the ease of expectoration or the severity of the asthma. A roentgen-ray of the chest two years ago showed bronchial markings increased, mainly in the lower lobes, and no suspicion of tuberculous lesions. Twice in the past three years the patient had had symptoms of dyspnea on exertion and had responded well to a therapeutic test of digitalization.

Present Illness: On November 28 the patient felt a sense of oppression in the chest and noted that his asthma was not as well controlled by his prescription of ephedrine and phenobarbital as usual. His sputum, usually raised without difficulty, became brownish, "very sticky," and "hard to bring up." On November 29 he felt feverish and very dyspneic. Examination then showed a very dyspneic man of 70, not cyanotic, T. 38° C., P. 76, R. 32, and B.P. 126/62. His chest was of the emphysematous type and filled with sonorous and sibilant rhonchi throughout. There were a moderate number of moist râles at the bases. Present also were dullness and transmission of whispered voice sounds over the upper division of the right lower lobe. The liver was palpable two fingers'-breadth below the right costal margin. The sputum was a homogenous brick-red, very thick, and peculiarly sticky and stringy. The Gram stain showed great numbers of large Gram-negative encapsulated rods and a very rare Gram-positive coccus. A pure culture of Friedländer bacillus of Julianelle's Type A was recovered. The only urinary abnormality was a two-plus acetone. The sedimentation rate by Linzenmeier's method was 18 mm. in 50 minutes. There were 12,200 white blood cells, with 82 per cent neutrophiles.

Progress and Treatment: Epinephrine 1:1000 hypodermically was administered frequently. In asthma-free intervals the classical signs of consolidation were obtained over the upper portion of the right lower lobe. Small doses of quinine controlled the chills that the patient started to have. Dyspnea unrelieved by adrenalin, an increase in basal râles, a lowering pulse pressure (B.P. 100/54), and an occasional extrasystole on the second day suggested a weakening myocardium. Digitalization was rapidly effected and maintained throughout the illness, with benefit to the dyspnea, reduction of the râles, and maintenance of the blood pressure up to an average of 130/64 for the remainder of the illness. The height of the fever was reached on the fifth day and was maintained until the twelfth day. The temperature swung from 36.4° C. to 39° C. daily; the respirations varied from 26 to 38 (depending on the amount of adrenalin effective at the time), and the pulse remained at 94 to 100. The right lower lobe became completely consolidated by the fifth day, and a suspicious patch had appeared in the left lower lobe posteriorly.

From the very beginning sodium citrate had been given for the dual purpose of counteracting acidosis and liquefying the sputum. Although the ketonuria was kept to a minimum and the urine usually alkaline to methyl-red indicator, the expectorant effect was nil; the consistency of the sputum remained unchanged. On the fifth day, therefore, it was decided to try the effect of stopping sodium citrate and using sodium iodide to the limit of tolerance as judged by rhinorrhea. The effect was remarkable: the sputum became much thinner and was brought up with ease; adrenalin became necessary only infrequently; the subjective condition of the patient improved immediately; and the signs disappeared from the left lower lobe. By the eighth day, however, a mild acidosis was evident clinically and the ketonuria was marked. Sodium citrate was substituted for the sodium iodide; the acidosis was checked but the sputum became thick and sticky again. Adrenalin became necessary frequently, and the patient felt much worse. Examination on the tenth day showed the right lower lobe consolidated, and slight dullness with moderate diminution of breath sounds over the left lower lobe. The left diaphragm was apparently elevated also. Sodium citrate and sodium iodide were then administered together, with the same spectacular effect previously noted. The signs over the left lower lobe were gone by the next

day. On the thirteenth day the temperature was only 37.6° C., and on the next day came to normal and stayed there. The pulse and respiratory rate came to normal on the twenty-third day of the illness. The chest was negative to physical examination, except for the customary faint rhonchi, by the twentieth day.

TABLE IV

Laboratory Observations

Time	Sputum	Blood Culture	Agglutinins	Urinary Acetone Bodies	Urinary Albumin	Linzenmeier Sed. Time to 18 mm.	W.B.C.	% Neutrophiles
21 days before onset	—	—	—	0	0	145 min.	7,800	64
2nd day	Pure culture of Friedl. bac.	—	—	++	0	50 min.	12,200	82
4th day	—	Neg.	None	+	0	36 min.	15,700	85
6th day	Pure culture of Friedl. bac.	—	—	+	0	—	—	—
9th day	—	—	1 : 80	+++	+	20 min.	18,000	88
11th day	—	Neg.	—	+	+	—	—	—
13th day	—	—	1 : 320	0	+	18 min.	18,700	85
17th day	Strep. mic. catarrh. Friedl. bac.	—	1 : 640	0	0	26 min.	11,200	78
23rd day	—	—	—	0	0	52 min.	8,300	62

Certain features of this case are of interest. The recovery, in spite of the advanced age of the patient and the associated bronchial asthma and degenerative myocarditis, is noteworthy. Only 21 days before the onset of his illness he had been given a routine check-up, and his white blood count and sedimentation rate were known. In pneumonia due to the pneumococcus, streptococcus and Pfeiffer bacillus the Linzenmeier sedimentation rate by the second day is practically always below 30 minutes. The rapid development of specific serum agglutinins recalls the observations of Bhatnagar and Singh,[12] who noted the development of agglutinins to 1 : 1000 in their recovered case but never above 1 : 100 in their fatal cases. Specific serum treatment would have been attempted, but no serum was obtainable at that time in the San Francisco Bay area. Oxygen therapy was tried on the sixth day, but no benefit was noted and it was discontinued. The spectacular effect of iodide administration and its possible significance will be discussed later.

FACTORS AND TREATMENTS LEADING TO RECOVERY IN PRIMARY FRIEDLÄNDER PNEUMONIAS

A consideration of table 3 and a comparison of it with our knowledge of similar data in fatal cases allow the following conclusions. The average age of recovered cases is 39; this speaks for relative youth as a significant factor, as the average age of fatal cases is approximately 50. About one-half of fatal cases have a leukocytosis, the remainder having normal or subnormal counts; all except one of the recovered cases reported had a leukocytosis. Whereas only one-third of fatal cases had negative blood cultures, three quarters of the recovered cases had negative ones. Agglutinin determinations were available in only a few cases, i.e., in Bhatnagar's and some of Solomon's fatal cases (17), and in Bhatnagar's and the author's recovered cases (two). It is of in-

terest to note that in none of the fatal cases did the agglutinins, if present at all, go above 1 : 100, but that in the two recoveries the agglutinins reached 1 : 640 and 1 : 1000. The administration of intravenous colloidal silver and of trypflavine have been shown to be useless gestures in other types of bacterial infection, and the two cases mentioned probably recovered in spite of these measures rather than because of them. The disease is too fulminating to permit of vaccine therapy, the patients already producing their own vaccine. Routine supportive and symptomatic therapy (including oxygen), so important in all pneumonias, has been supplemented so far only by surgery, specific serum, and iodides. In reviewing the fatalities one is struck by the number of cases complicated by empyema and pulmonary abscess undiagnosed during life. Appropriate drainage by surgical means would probably have saved some of these lives. The claim might be made that these patients are too sick to stand diagnostic and therapeutic procedures, particularly surgical ones, but our present 94 per cent mortality by conservatism indicates that we probably have much more to gain than to lose by apparent radicalism.

Serum treatment of Friedländer pneumonia is in its experimental stage. Theoretically it is the ideal treatment. Practically, there are difficulties in the way of its universal application. The serum is available only in a few eastern centers. Diagnoses of Friedländer pneumonia (during life) are so infrequent that no one investigator can make a critical evaluation of serum treatment from personal experience, and the likelihood of deterioration of the serum to nil potency between cases is a real one. Neither public nor private institutions like to assume the expense of having on hand at all times fresh stocks of a serum for which they have infrequent calls. Like all therapeutic sera, it should be given early to be most effective; airplane service, if used, would help realize this aim. Judging from our past experiences with sera for even the common diseases, the cost will be prohibitive for some time to come. Three recoveries in six of Bullowa's (Haarlem Hospital) cases in which the serum was given early enough to be effective may be only coincidence, but the report certainly is encouraging.

To make any generalizations on the usefulness of iodides on the basis of one case is unscientific. The effect, however, was interesting. Its use in the reported case was prompted by a study of the pathology of Friedländer pneumonia. In pneumococcal, streptococcal and influenzal pneumonias we have to deal with a parenchymatous process practically from the onset. The stages of engorgement, red hepatization, gray hepatization, and resolution affect each area usually in uncomplicated sequence; atelectasis and bronchial inflammation are minor features. With Friedländer bacillus pneumonias, in addition to this classical picture, there is a significant bronchial and bronchiolar involvement. The peculiarly sticky, stringy exudate which we later see as sputum blocks the smaller and often the larger air passages. The resulting areas of atelectasis undergo secondarily both the classical pneumonic and the necrotizing types of inflammation. Although useless in other types of pneumonia, a liquefying expectorant can evidently be of value in the Friedländer type. The patient should be enabled to dispose of his bronchial exudate with ease, with a resulting prevention of atelectases and a conservation of effort. The reported case is the first in which liquefying expectorant therapy in primary Friedländer bacillus pneumonia was tried. In actual practice we are limited to three types of liquefy-

ing expectorants; i.e., salts of citric acid, ammonium chloride, and hydriodic acid with its sodium and potassium salts. In this case the expectorant effect of citrates was not evident even in large doses. Ammonium chloride has the disadvantages of furthering acidosis and providing a larger nitrogen burden for the kidneys, and consequently was not even tried.

Summary

1. Approximately 5 per cent of normal people carry the Friedländer bacillus in their upper respiratory tract.

2. Acute primary Friedländer bacillus pneumonia comprises, on an average, 0.76 per cent of all acute primary pneumonias.

3. Only 284 cases of genuine Friedländer bacillus pneumonia have been mentioned in the medical literature from 1882 to 1938.

4. In only 233 cases are satisfactory clinical records or summaries available.

5. Of these 233 cases, 219 were fatal. The mortality rate is 94 per cent.

6. Only 13 recoveries have been reported previous to the author's case.

7. The author's patient contracted his illness at the age of 70 and is the oldest known patient to have recovered.

8. Significant clinical data on the 14 recoveries are summarized.

9. The author's case is reported in detail, with complete laboratory investigation.

10. Only surgery for complications and serum have thus far been helpful as additions to routine supportive therapy.

11. The use of iodides in the author's case and its rationale are reported.

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CONSTITUTIONAL REACTIONS FROM BACTERIAL VACCINES *

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The recent communication of Brown [1] indicates that constitutional reactions from bacterial vaccines *never* resemble those occurring from injections of protein extracts. Herewith is reported an exception, the only one I have observed in 240 asthmatics treated with bacterial vaccines.

Case Report

E. J. D., male, aged 12, with a history of winter asthma of bacterial origin since the age of three, and under my care since the age of six, in the fall of 1937 gave a very strong immediate whealing reaction from the intradermal injection of 0.02 c.c. of Squibb's Catarrhal Vaccine No. 5. A moderately strong direct reaction to house dust was also present. All other direct tests with foods and inhalants were negative. Passive transfer was negative for all excitants, including both the dust and the vaccine.

Pre-winter treatment, with weekly alternating doses of dust and vaccine was begun, each dose being increased by 0.05 c.c. Two minutes after the subcutaneous injection of the 0.35 c.c. dose of the vaccine (with suction precaution) a severe explosive constitutional reaction of the protein extract type occurred; the symptoms developed were itching and swelling of the conjunctivae, itching of the nose and throat, sneezing, dyspnea, suffocating cough and urticaria. One week later, the dose of 0.35 c.c. of the vaccine was repeated, and the immediate constitutional reaction, though not so severe, again occurred. Treatment was discontinued and the patient

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had no asthma during the winter. Direct skin testing with Squibb's Catarrhal Vaccine No. 5, and with the *Staphylococcus aureus* and *Staphylococcus albus* therein (E. R. Squibb Co. kindly supplied me with the individual components of their mixed respiratory vaccine) have remained strongly immediately reactive, but passive transfer has failed. The patient has since developed spring hay-fever due to grasses, and both the direct and indirect reactions are present to this atopen.

Summary

A case of respiratory allergy is reported in which repeated immediate constitutional reactions of the explosive type occurred following the subcutaneous injection of a stock vaccine. Repeated efforts passively to transfer the reaction of the vaccine to the skin of a substitute failed. Mention is made of this effort to transfer the reaction by the Prausnitz-Kustner technic because of the moot question of the transferability of bacterial reactions.

Conclusion

That the explosive type of constitutional reaction following the injection of bacterial vaccines is rare, but does occur, is the conclusion drawn.

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MYCOTIC ANEURYSM; REPORT OF ONE CASE*

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Case Report

R. C., a white male, 43 years of age, was seen on December 10, 1935, complaining that for two days he had been having severe head pain in the right frontal area. He had been ailing since August 1935, when he had developed cerebro-spinal meningitis. At that time he had been treated by spinal drainage and instillation of four doses of serum. He had recovered in four weeks, but had continued to feel very weak. About October 1 he began to feel pain in his joints, particularly in the knees and hips, and running down into his feet. His feet felt stiff when he arose in the morning, but after moving about they would gradually loosen up. Pain developed in the right kidney area and radiated to the right groin. He ran an elevated temperature, with chills. He complained of urinary frequency, and the urine contained pus. A cystoscopic examination showed only a kinked ureter, and following the examination the complaints of frequency and kidney pain ceased. A few days before the visit of December 10 he had a tooth extracted because of pain in the right upper jaw and in the right side of the head. There was not much bleeding at the site of the extracted tooth. On December 8 he developed headache which was located over the right eye and right frontal area. The pain became very severe, and, as the severity increased, he noticed difficulty in the use of his left upper extremity. The morning of Decem-

* Received for publication March 21, 1940.

ber 10 his pain was so severe that he could not sleep and had one vomiting spell. Review of history by systems revealed further that for the past month he had had frequent chills and felt cold most of the time; his appetite was poor, and the bowels were constipated; his strength had been gradually failing; and his weight had dropped from 160 to 140 pounds.

The past medical history included the usual childhood diseases. He had had bronchopneumonia while in France during the war, and scarlet fever in 1918 at Camp Grant. Cerebrospinal meningitis in August 1935 had left some deafness of the left ear. A herniotomy had been performed 10 years previously, and a finger had been amputated during boyhood due to a corn-shredder accident.

The family history revealed that the mother had suffered a cerebral hemorrhage, and one brother had died with tuberculosis. The social history contained nothing of interest.

On examination the patient appeared as a tall, slender, anemic male who walked with a tendency to fall to the left. He was fairly well nourished, and mentality was

FIG. 1. Recanalized, partially hyalinized thrombus with necrosis of wall and rupture of cerebral artery.

fair, except that he appeared drowsy. The temperature was 98.6° F., pulse 64, and respirations 16. There was tenderness and relative dullness over the right frontoparietal area, and orbital tenderness was present on this side. The pupils were equal and reacted to light and accommodation. The left ear was partially deaf. The nose and the eyegrounds were normal. The left side of the mouth was somewhat dropped. The teeth bore fillings, and some were missing. The tonsils were absent.

A slight rigidity of the neck was observed and the head could not be flexed upon the chest. The submaxillary nodes were palpable, but the glandular system was otherwise negative. The pulse was slow, and the blood pressure was 106 mm. Hg systolic and 90 mm. Hg diastolic. The chest was long and thin, and the lungs clear. There was left-sided cardiac enlargement, and a mitral systolic murmur. The abdomen was not abnormal except for a herniotomy scar on the left. The skin was normal. The findings in the neuromuscular system were outstanding: There was hemianesthesia of the entire left side, and partial motor paralysis of the left upper and lower extremities. The left side of the face was dropped slightly, and on this side the patient was able to show his teeth less well than on the right. Reflexes were relatively increased on the left, and Babinski's and Gordon's signs were present. A positive Kernig's test was elicited. The spinal fluid on lumbar puncture was bloody and under

slightly increased pressure. On the basis of the history and initial findings it was felt that the diagnosis lay among the following: (1) subarachnoid hemorrhage from a small vessel; (2) cerebral abscess as a sequel to cerebrospinal meningitis; (3) bacterial endocarditis with ruptured mycotic aneurysm.

The patient was put to bed at once on December 10, 1935, and morphine sulphate, gr. ¼, was given p.r.n. for pain. Since this was believed to be a case of subarachnoid hemorrhage, a second spinal puncture was done the same day. The fluid was bloody, and contained 153 white blood cells per cu. mm., with the lymphocytes predominating. For therapy two spinal punctures were ordered daily, and fluids were forced by mouth

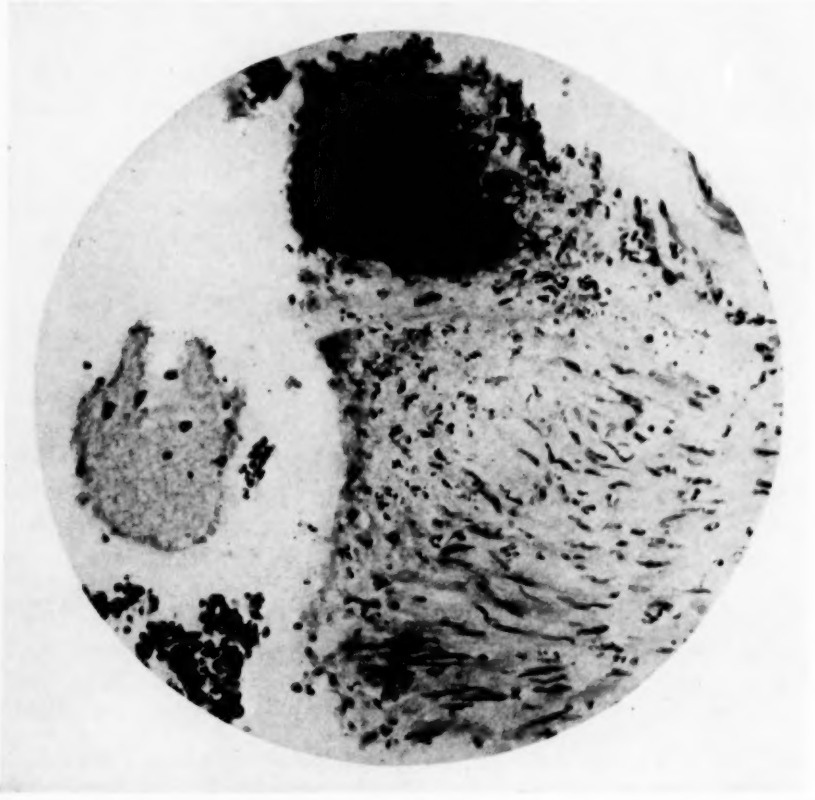

FIG. 2. Necrosis of artery wall at site of rupture, with embolus containing bacteria attached to intima.

and hypodermoclysis. Because the spinal fluid was very bloody, the temperature not elevated, and the white blood cell count only 9,200, the diagnosis of cerebral abscess was discarded. A roentgen-ray of the skull gave no evidence of tumor or other pathologic condition. The motor paralysis of the left side became more extensive and began to exhibit spasticity. During the course of the first week the patient became completely paralyzed on the left and at the same time very irrational. The temperature began to rise on the fourth day, and the elevation continued intermittently. The spinal fluid cleared on the sixteenth tap. A culture of the fluid gave no growth. A blood culture on December 18 gave a positive growth and the smear showed streptococci. The following three blood cultures were positive, and therefore a definite

diagnosis of subacute bacterial endocarditis with ruptured mycotic aneurysm was made. Blood transfusions were tried to combat the progressive infection and anemia. Intravenous medication with sodium cacodylate in five grain doses was started on December 25, 1935, and 10 injections were given.

The progress of the patient was steadily downward. The delirium, fever and pulse rate increased. Petechiae appeared on many parts of the body. Joint redness and swelling occurred, and motion in the affected joints was very painful. The fluid intake and output were fairly constant, although the urine contained blood. The spleen and liver became palpable and very tender. The white blood cell count rose

FIG. 3. Dense polymorphonuclear cell infiltration of artery wall adjacent to site of rupture.

on December 20 to 19,000 with 83 per cent neutrophiles, but fell to 7,000 on January 6, 1936, with 82 per cent neutrophiles. After a long period of increasing helplessness, mental confusion, and cardiac weakness the patient died on March 6, 1936. The final clinical diagnosis was: (1) subacute bacterial endocarditis; (2) ruptured mycotic aneurysm of artery in right cerebral hemisphere.

AUTOPSY REPORT

Anatomical Diagnosis: Acute vegetative endocarditis of mitral valve; pericarditis with effusion; bilateral confluent bronchopneumonia; multiple cerebral artery em-

bolism with thrombosis and encephalomalacia; necrosis of wall of the cerebral artery with rupture, hemorrhage and cyst formation; multiple infarcts of the spleen with degeneration and liquefaction; bilateral infarcts, both recent and old, of the kidneys; multiple petechial hemorrhages of the mucous membranes and skin; marked emaciation.

The body was markedly cachectic, with scattered petechiae and ecchymoses in the skin over the abdomen and chest, the hemorrhages measuring from pin-point size to 3 mm. in diameter. The conjunctivae were studded with petechiae.

The lungs were partially collapsed. Both pleural cavities were free of fluid. The superior lobe of the right lung was crepitant throughout, while the middle and

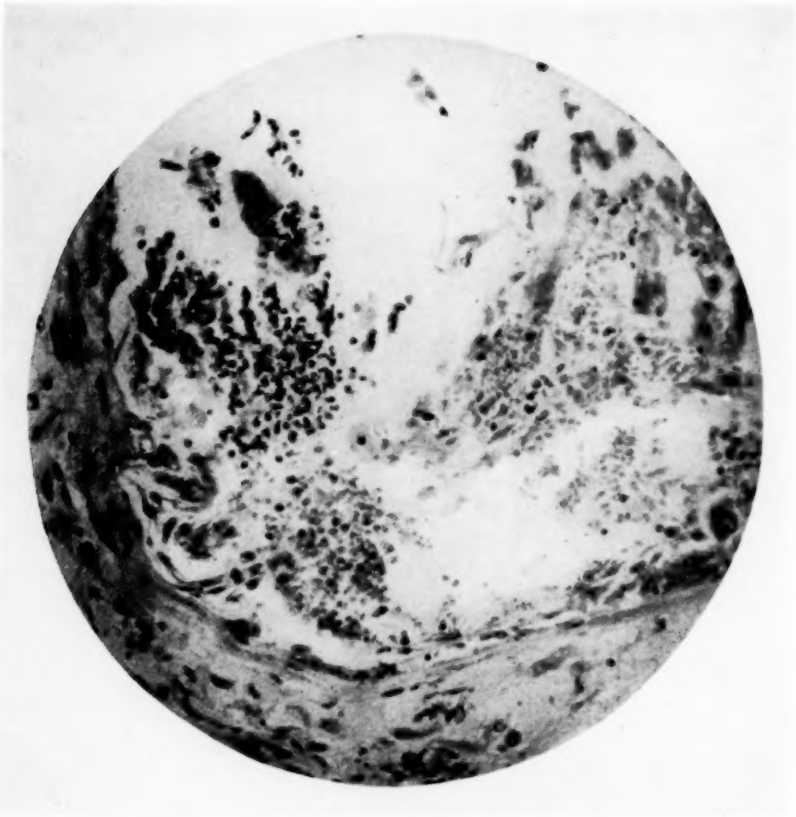

FIG. 4. Infected embolus of artery wall partially recanalized.

lower lobes were discolored, mottled, bluish-red, heavy and firm. The cut surface was very wet, dripping frothy exudate, and was grayish-red in color, having the appearance in portions of gray hepatization. The left lung was similar to the right.

The pericardial sac was greatly distended and contained about six ounces of clear, straw-colored pericardial fluid. The heart was in systole. The visceral pericardium was somewhat thickened with gray patches. The heart weighed 340 grams. The mitral valve ring measured 10 cm. in circumference. The anterior leaflet was covered by a thick, verrucose vegetative growth that covered the distal half of the leaflet, and extended upward over the lateral left auricular wall over an area measuring 5.5 cm. in diameter. This vegetative growth extended downward onto the chordae

tendineae and anterior papillary muscle. The growth had confined itself mainly to the anterior leaflet. There was no evidence of calcification. The left ventricular wall measured 1.5 cm. in thickness in the middle third. The aortic ring measured 7.5 cm. in circumference. The aortic valve leaflets were grossly normal, and the endocardium was smooth and normal, down to the mitral ring. The pulmonic valve measured 7 cm. in circumference, and the valve leaflets were grossly normal.

There was no free fluid in the peritoneal cavity. The omentum was almost entirely devoid of fat. The intestines, including the stomach and large bowel, were collapsed and grossly normal. The gall-bladder was distended with bile and the bile ducts were patent. The spleen was adherent to the stomach, was surrounded by the omentum, and was also adherent to the peritoneum by dense, fibrinous adhesions. It was very much enlarged and weighed 365 grams. On the lower pole there were two large, discolored areas measuring 2 and 1.5 cm. in diameter. The capsule was tense, and the entire organ felt soft. The cut surface revealed the two areas in the lower pole to be large infarcts, measuring 2 by 3 and 1.5 by 2 cm., gray-red and firm. In the center there was a large infarct measuring 5 cm. in diameter, which had undergone degeneration and liquefaction. There were numerous smaller infarcts scattered through the parenchyma. The liver weighed 1400 grams, and was normal in all respects. The right kidney weighed 125 grams and the left weighed 140 grams. The surface was studded with grayish and hemorrhagic areas, varying from 6 to 8 mm. in diameter. The cut surfaces revealed the cortex and medulla studded with numerous infarcts, some of which had undergone fibrosis and others of which were hemorrhagic. The capsule stripped with some difficulty, especially overlying the infarcts. The lining of the pelvis was studded with petechial hemorrhages. The left kidney was similar.

Brain: There was old blood pigment staining over the membranes covering the right occipital and parietal lobes and over the inferior surface of the left temporal lobe. A blood clot was present about the vessels in the left Sylvian fissure. There was a thrombus at the bifurcation of the left middle and posterior cerebral arteries beyond which point there was an area of encephalomalacia involving the tissue adjacent to the Sylvian fissure. On multiple transverse section of the brain it was revealed that the encephalomalacia involving the tissue adjacent to the left Sylvian fissure was rather superficial, but adjacent to the base on the left it extended more deeply into the underlying tissue. In this area are multiple small thrombosed vessels. Anteriorly on the right and immediately lateral to the thalamic tract was a thrombosed vessel with rupture and extravasation of blood cells into the surrounding tissue for an area 3 cm. in diameter. In the gray matter of the right temporal lobe was situated a cavity approximately 2 cm. in diameter filled with old blood, soft in consistency and lined by yellowish membrane, tapering to an area pointed in shape anteriorly and posteriorly with softened brain tissue surrounding and extending to a distance of about 6.5 cm. The area of hemorrhage lay immediately beneath the lateral surface of the right lateral ventricle. The lining of the right lateral ventricle showed congested vessels. Section of the pons and medulla showed no gross changes.

Microscopic Diagnosis. Section of the brain showed an area of necrosis and old hemorrhage with a border of phagocytes containing iron pigment, occasional polymorphonuclear and round cells. In the same section was a large artery with hyalinized areas of intima, a hyalinized and recanalized thrombus and an infected embolus consisting of bacteria plus polymorphonuclear and round cells.

Section of kidney showed multiple emboli of the glomeruli.

The lung exhibited bronchopneumonia and edema.

The liver showed chronic passive congestion and miliary abscesses.

The spleen exhibited infarcts with central abscess formation, and chronic passive congestion.

Discussion

Descriptions of mycotic aneurysms are uncommon in medical literature, and clinical diagnosis of their presence prior to autopsy is very rarely made. Such aneurysms develop in the course of a bacteremia, which may be of any origin, but most commonly that associated with bacterial endocarditis. The infecting organism may be any one of many varieties. The affection occurs during the earlier years of life rather than in middle life and old age. The heart, aorta, medium-sized and small arteries may be involved, and involvement of veins [1] has been described as well. According to Reifenstein,[2] the first description of an embolomycotic aneurysm was apparently made by Koch in 1851, his case being that of a ruptured mycotic aneurysm complicating an acute endocarditis. Ponfick, Pel, Osler and others have since reported additional cases and have described the method of formation of the aneurysm. In the smaller vessels the condition is due to the direct lodgement of infected emboli, often at the bifurcation of the small arteries. Infection and erosion of the artery wall follows, and an aneurysm is produced by pressure on the weakened vessel. Osler [3] states that the process is favored in vessels which receive little support from surrounding tissues; hence, the frequent occurrence of such aneurysms in the mesenteric, cerebral and the more superficial peripheral arteries. The process differs in the case of the multiple mycotic aneurysms of the aorta, which in all probability usually arise from emboli in the vasa vasorum. Symptoms are likely to arise during the stage of inflammation of the vessel wall, if the vessel be superficial, consisting of pain and swelling at the site. On the other hand, in an organ such as the brain, symptoms arise in the event of rupture of the aneurysm. In many cases no symptoms are noted, and the condition is recognized only at autopsy or not at all.

The present case was one in which a diagnosis on the basis of clinical and laboratory findings was possible before death. A man of 43 presented the picture of sudden onset of hemiplegia restricted to the right cerebral hemisphere, increased intracranial pressure, and prolonged hemorrhage into the subarachnoid space. On the other side of the picture was the gradual increase in weakness and weight loss, the chills and fever, a mitral murmur, the embolic phenomena, and a positive blood culture completing the story of subacute bacterial endocarditis. Considered with the rest of the history, these circumstances justified the diagnosis of ruptured mycotic aneurysm of a cerebral artery, which was verified at autopsy. The remainder of the autopsy picture was that commonly seen in cases of subacute bacterial endocarditis.

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PARATHYROID TETANY: CHRONIC IDIOPATHIC PARATHYROID INSUFFICIENCY OF TEN YEARS' DURATION SUCCESSFULLY CONTROLLED WITH DIHYDROTACHYSTEROL *

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CASE REPORT

The patient was a young woman, 23 years of age, who was admitted to the Long Island College Hospital for the first time in April 1932. At that time she was 17 years of age and her presenting complaint was convulsions.

The family history was irrelevant. Her past history revealed scarlet fever at four years, right mastoidectomy at seven years, measles and chickenpox at 10 years.

Her present illness began with the onset of her menstrual cycle at 14 years of age in the summer of 1929. Forty-eight hours after the onset of her first period she developed tetany with carpopedal spasm. When this recurred for several menstrual periods she entered Bellevue Hospital where she was successfully treated with calcium and viosterol. The patient remained well until November 1930 when the tetany returned at the time of her menstrual period. On this occasion she had her first convulsive seizure. She stated that a certain word kept repeating itself in her mind and then she lost consciousness. According to the description given by her family there was a carpopedal spasm followed by clonic shaking movements of her arms and legs lasting one-half to one minute. After the convulsion she was drowsy for an hour. It was noted that she had bitten her tongue. These convulsions recurred at her next three menstrual periods. In February 1931 she had convulsions several times a day and night during her menstrual period. She was admitted to Bellevue Hospital where a diagnosis of epilepsy was made. The patient was placed on bromides, a high fat diet, and restricted water intake. After two months' treatment she was so improved that she was free of any convulsions until January 1932. Then, the convulsions recurred at the time of the menstrual periods and in April 1932 she was admitted to the Medical Service of the Long Island College Hospital on the service of Dr. E. R. Marzullo. The physical examination showed her general condition to be good. Typical tetany was present and the Chvostek and Trousseau signs were easily elicited. There was evidence of some loss of hair but no evidence of cataract or dental deficiency. The thyroid was just palpable. Her laboratory data aside from the calcium study were normal. Her blood calcium was 5 mg. and phosphorus 10 mg. per 100 c.c. The spinal fluid calcium was 4.5 mg. The alkaline reserve was 54.6 per cent. With the administration of 20 units of parathormone daily the blood calcium rose to 10.8 mg. and the phosphorus fell to 5.2 mg. in 17 days. She was discharged on a high calcium diet, calcium gluconate and viosterol but the parathormone was omitted. At the next menstrual period she was again in difficulty with tetany and epilepsy and she was readmitted to the hospital.

Between May 1932 and February 1933 the patient had four hospital admissions during which many investigations were conducted. We also followed her in the Out-Patient Department and kept a close record of her calcium metabolism. A summary of the findings follows. The gastric analysis, gastrointestinal roentgen-rays, and barium enema were normal. The basal metabolism averaged minus 5.1 per cent to plus 4.5 per cent. Roentgen-rays of the skull, the long bones, the ribs, and the teeth were normal. The sugar tolerance was normal. The routine blood chemistry was

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normal. These additional findings on the blood chemistry were normal: alkaline reserve 51 per cent, chlorides 575 mg., total protein 7.11 mg., serum albumin 4.43 gm., serum globulin 2.68 gm. The average readings for the blood calcium were 7.5 mg. and for phosphorus 7 mg. With the onset of menstruation the calcium dropped to 6 mg., the phosphorus rose to 9 mg. and tetany would appear. In another day or two the calcium was reduced below 6 mg. and convulsions occurred. The blood calcium remained at a low level for a week after menstruation and at this period also convulsions occurred. The administration of parathormone during the menstrual period prevented this marked drop in calcium. For example, on one occasion when 20 units of parathormone were given daily for two days premenstrually the blood calcium was 9.5 mg. and the phosphorus was 5.6 mg. at the onset of menstruation. With the continued daily injection of parathormone the blood calcium was 8.2 mg. and the phosphorus 7.3 mg. at the end of a five-day menstrual period. The menstrual periods were irregular, often 10 to 14 days over the usual 28 day cycle. The flow was scant although it lasted for five days. A study of the calcium metabolism [1] revealed retention of calcium in her body, amounting to 0.98 gm. of calcium per day. When the experiment was repeated and 20 units of parathormone were administered daily there was an increased excretion of calcium. The increased excretion was mainly in the urine, bearing out the experience of Albright, Bauer, Ropes and Aub.[2]

Attempts to keep the blood calcium elevated by means of various calcium preparations in large doses by mouth met with failure. A low phosphorus diet plus large amounts of calcium by mouth was unsuccessful. Ammonium chloride in large doses was of no avail. Viosterol up to 3 c.c. daily did not help. Parathormone had to be used to keep the patient out of difficulty. It was usually given about two days before the expected period, during the menstrual period and for a few days after. From February 1933 the parathormone was used regularly at each menstrual period. The initial dose was 20 units daily but it was soon found, in accordance with the experience of others, that the dose of parathormone subcutaneously had to be increased. Within a year even up to 100 units twice a day did not keep the patient from tetany and convulsions.

In March 1934 the patient went to Johns Hopkins Hospital where Dr. Owings did a parathyroid graft by his special technic. This was unsuccessful and in May 1934 the procedure was repeated. The patient improved and did not require parathormone for almost one year. In April 1935, however, her difficulty recurred and she was admitted to the Long Island College Hospital in July 1935. At that time the patient had a definite psychoneurosis. She would not get out of bed because of the fear of a convulsion. She was placed on a low phosphorus diet with calcium gluconate by mouth. Parathormone was again administered at the menstrual period, the average dose being 50 to 100 units daily. For the next two years the patient did fairly well. She was disturbed by mild carpopedal spasm at the time of her menstrual period. An increase in the dose of parathormone apparently was not needed.

In June 1937 the patient married. She became pregnant shortly afterward and did very well during her pregnancy. The blood calcium in the fifth month of her pregnancy was 8.8 mg. She was able to carry on full physical activities for the first time in nine years. She was delivered of a normal infant on March 22, 1938. Two days afterward the blood calcium was 8 mg. and the phosphorus 6.1 mg. A week later the calcium was 6.6 mg. and the phosphorus 7.3 mg. The patient did not nurse the baby and about one month after delivery the menstrual period returned with the attending tetany and convulsions.

Her recurring difficulty at each menstrual period necessitated readmission to the hospital on November 22, 1938. The patient showed the usual signs of tetany and she was very apprehensive. A slit-lamp examination by Dr. Robert M. Rogers showed beginning cataract formation. The blood calcium was 6.5 mg. and the phos-

phorus 6.9 mg. At this time it was decided to use a new drug, dihydrotachysterol—also known as AT10. Eight ounces of a 5 per cent calcium lactate solution were given daily. With an average dose of 1.5 c.c. of dihydrotachysterol daily the blood calcium rose to 8.7 mg. and the phosphorus fell to 4.6 mg. in six days. On the twelfth day of therapy the menstrual period began and the blood calcium dropped to 7.9 mg.; the phosphorus was unchanged. The dose of dihydrotachysterol was increased to 3 c.c. daily for two days and then dropped to 2 c.c. daily. By the end of the menstrual period on the seventeenth day of therapy the blood calcium was 10.3 mg. and the phosphorus 4.69 mg. During this period the patient felt well and she learned to get around without any fear of calamity. On the nineteenth day she returned home and has continued to do well. She not only takes care of her own home and child, but has even been able to partake of physical exertion such as skating. The medication has consisted of six ounces of 5 per cent calcium lactate solution and 20 minims of dihydrotachysterol daily.* During the menstrual period the dihydrotachysterol is increased to 21 minims. Her diet has been a full one, including milk, cheese, meats and vegetables. On April 26, 1939, two days after her last menstrual period, the blood calcium was 9.5 mg. and the phosphorus 5.5 mg. We have asked the patient to reduce the milk and cheese in her diet in order to lower the blood phosphorus.

Comment

It was felt that the patient was suffering from idiopathic parathyroid insufficiency with tetany. The convulsive seizures were due to the low blood calcium allowing a marked irritability of the nervous system to occur. At no time did the patient have a convulsion when the blood calcium was 7 mg. or over. Greenwald and Gross [3] observed that calcium excretion was decreased after parathyroidectomy. In parathyroid deficiency the calcium apparently leaves the blood to be deposited in the tissues,[4] perhaps the bones. In the reported cases no increased density of the bones was observed, but roentgen-rays may not be sufficiently delicate to show the increased deposit of calcium. The occurrence of the symptoms at the time of the menstrual period brought up the question of the influence of the internal secretion of the ovary on the calcium level. The experimental work of Luckhardt and Goldberg [5] showed that there was a physiological antagonism between the ovaries and the parathyroids. These workers treated completely parathyroidectomized dogs with sufficient calcium lactate to prevent tetany but the animals showed a recurrence of all the symptoms of tetany at the time of oestrus. More recently Mathieu [6] has shown that in thyroparathyroidectomized dogs with intact ovaries, the injection of a gonadotropic substance from the urine of pregnant women produced typical oestrus. At the same time there was a marked reduction in the blood calcium and severe tetany ensued. In certain cases the tetany was manifested for as long as 15 days after the injections. In thyroparathyroidectomized dogs without ovaries the injection of gonadotropic substance did not reduce the blood calcium. It also was without influence in the thyroparathyroidectomized male dog and in normal dogs.

Holtz [7] described tachysterol as one of the products of the irradiation of ergosterol. It is less toxic than the others. A dihydro derivative, dihydrotachysterol has a marked effect in elevating the blood calcium. It is not antirachitic. The drug is available in the form of a clear oily solution which is stable indefinitely and is administered by mouth. Its action is similar to parathyroid extract

*The patient has continued this routine and the last blood study on July 11, 1940 revealed a blood calcium of 9.5 mg. and a phosphorus of 3.63 mg.

but it acts more slowly and over a longer period of time. The first increase in blood calcium is noted in about 48 hours, and with small doses a normal blood calcium is reached in seven to 14 days. The blood phosphorus shows a slight initial rise, then falls as the calcium approaches normal. The effect on the calcium persists for one to three weeks after discontinuation of the drug. Only small amounts of the drug are necessary after a normal blood calcium is reached and frequent determinations of the blood calcium must be made before the maintenance dose is established. Mac Bryde [8] recently reported the successful treatment of seven cases of parathyroid tetany with dihydrotachysterol. These patients have been kept free of symptoms for some period of time.

Overdosage with dihydrotachysterol causes the same toxic effects as overdosage with parathyroid extract and these are attributable to hypercalcemia The early symptoms are anorexia, nausea, vomiting; these are followed by headache, thirst, stupor, ataxia, and exanthems. The drug should be stopped. the patient should be at complete bed rest and large amounts of fluid administered both by mouth and parenterally.

Conclusion

A case of chronic idiopathic parathyroid insufficiency of 10 years' duration complicated by convulsions at the time of menstruation has been remarkably improved by the use of dihydrotachysterol. All types of calcium therapy and diets, parathyroid extract and parathyroid gland grafts, though of some temporary benefit, were ultimately inadequate. This case bears out the experience of others in that dihydrotachysterol is very successful in the treatment of parathyroid insufficiency.

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EDITORIAL

PLASMA PROTEINS

UNTIL recently, relatively little has been known as to the significance and real function of the plasma proteins. The part they play in maintaining the osmotic pressure within the vessels and in regulating the exchange of fluid between the capillaries and the tissue spaces has been established. It has long been known that the globulin of the plasma includes the various immune bodies active in combating infection, as well as the fibrinogen and the prothrombin concerned in blood coagulation. It was widely assumed that they did not enter directly into the metabolism of the body tissues generally. Their source and the mechanism of their formation has also been in dispute.

Much new light has been shed on some phases of this problem by recent investigations: such as those of Weech at Columbia, Melnick and Cowgill at Yale and, particularly, of Whipple and his associate at Rochester.[1] These studies have been carried out mainly on animals which have been largely depleted of their body proteins by protein starvation or by bleeding. The method employed by Whipple and his associates [2] is particularly ingenious and fruitful. They kept dogs on a standard diet containing approximately a minimum maintenance protein ration. By repeatedly bleeding the animals and restoring the red cells (washed and suspended in salt solution, plasmapheresis) to avoid producing an anemia, they were able to deplete the plasma proteins to any desired degree. They could maintain this diminished plasma protein level by adjusting the volume of plasma removed. They found that after this procedure had been kept up for several weeks, the amount of plasma which had to be removed to maintain the state was practically constant for the animal. Dogs in which the plasma proteins were thus kept at a constant level of 4 per cent were clinically normal in every other respect. The effect upon plasma protein formation which might be caused by alterations of, or additions to the diet or by other experimental procedures could be measured by the change in volume of bleedings required to maintain this constant level.

To synthesize protein the body requires proteins (or protein split products) from outside sources. The effectiveness of various foods was determined by adding them to the diet of such depleted dogs. As might be anticipated, there was considerable variation in potency. Much the most effective was beef serum, which might result in the production of plasma protein

[1] An excellent review, with bibliography is given by: MADDEN, S. C., and WHIPPLE, G. H.: Plasma proteins: their source, production, and utilization, Physiol. Rev., 1940, xx, 194–217.

[2] MADDEN, S. C., GEORGE, W. E., WARAICH, G. S., and WHIPPLE, G. H.: Blood plasma protein regeneration as influenced by fasting, infection and diet factors; variable reserve stores of plasma protein building material in dog, Jr. Exper. Med., 1938, lxvii, 675–690.

equivalent to 40 per cent of the serum protein eaten. Fairly effective were kidney, liver, casein, muscle, bran, and rice; heart, brain, spleen, stomach, and red blood cells were poor. The incomplete proteins, gelatin and zein, were inert.

The addition of certain amino acids to the diet also increased plasma protein formation—perhaps because they supplemented some relatively incomplete proteins in the diet. Cystine, leucine and glutamic acid were the most efficient and apparently the most important in this respect.[3] The rest of the nine or ten amino acids found necessary for growth in rats by Rose are probably also required, but direct proof of this is still lacking.

The site of synthesis of the plasma protein is still disputed. There is strong evidence that fibrinogen and prothrombin are formed only in the liver. Whipple believes that the albumin and much of the globulin are also found in the liver. This is based largely on the low plasma proteins formed after partial hepatectomy or experimental liver injury, and clinically in cirrhosis and allied conditions associated with liver injury. On the other hand antibodies—and possibly other globulins—are undoubtedly formed by the cells of the reticuloendothelial system generally.

The most interesting point brought out by these studies is that the plasma proteins constitute functionally an integral part of the general body proteins and are not isolated and independent substances. In a starving animal, homologous plasma protein injected intravenously will not only elevate the blood protein of the recipient but will maintain the animal in nitrogen equilibrium. Manifestly this protein has been seized by the body cells and utilized in their metabolism, and this is accomplished without any loss of nitrogen, as determined by a study of urinary excretion. On the other hand, if an animal which is fasting is bled so as to reduce the plasma protein sharply, there will be a substantial rise in plasma protein within a few hours, which may continue at a less accelerated pace for some days. This increment manifestly must come from protein or protein building materials from the tissues. This reserve store of protein is also shown by Whipple's experiments on standard depleted dogs, in that the amount of bleeding required to maintain hypoproteinemia is substantially greater during the first few weeks than in the later stages of the experiment. This excess protein so removed is a measure of the reserve stores of the body and may amount to from 100 to 200 per cent of the normal circulating plasma protein. The reserve store may also be depleted by protein starvation. It may be regarded as analogous to the body stores of carbohydrate (glycogen) and fat. Serious depletion of the stores results in lowered resistance to infection and to certain intoxications.

The exact nature and location of these protein stores is not definitely known. It can not be recognized histologically, like glycogen or fat. No

[3] MADDEN, S. C., FINCH, C. A., SWALBACH, W. G., and WHIPPLE, G. H.: Blood plasma protein production and utilization. The influence of amino acids and sterile abscesses, Jr. Exper. Med., 1940, lxxi, 283–297.

special type of protein which might be regarded as storage protein has been isolated. The liver has been regarded as a probable storage site. This view receives some support from the experiments of Addis, Poo and Lew,[4] who studied the amount of protein lost by various organs and tissues in starved rats. They found that the liver lost a larger proportion of its protein (40 per cent in seven days) than any other tissue, and that half of this was given up during the first two days. Conversely, when protein was fed, the concentration in the liver rose more rapidly and to a greater degree than in other tissues.

However, the amount of protein that can be withdrawn from the tissues in acutely depleted starving dogs may be greater than the total protein content of the liver, and it is obvious that other tissues participate in the process.

The nature of the stored material is not known. It seems improbable that it is in the form of simple amino acids. Some must be stored as plasma protein itself, since a substantial amount may be discharged into the plasma within an hour or two in an acutely depleted dog. A large part, however, is yielded up much more slowly; in fact, it appears to be no more promptly available than proteins in the food. It is thought, therefore, that it exists in some other form and requires resynthesis before it is available to the plasma. On the other hand the essential cellular proteins which may be regarded as part of the structure of the cells apparently do not contribute to the replenishment of plasma protein. Formation of the latter ceases in a depleted starved dog, although the nitrogenous by-products of cellular protein breakdown continue to be excreted in the urine. The body can not conserve these by-products and utilize them for new protein formation.

The importance of adequate stores of protein in maintaining normal health and nutrition indicates the advisability of supplying protein parenterally, along with carbohydrate and electrolytes, in patients who can not take them by mouth. This can be accomplished by the intravenous administration of homologous plasma since, as noted, it maintains nitrogen equilibrium in a starving animal, replenishes the reserve stores and raises the plasma proteins to normal. The protein, however, may pass out of the plasma into the tissues until the needs of the cells have been satisfied.

Recent work of Elman,[5] however, indicates that the body needs may be supplied by simpler materials. He subjected casein to hydrolysis, and to this added tryptophane and cystine or methionine, which were scanty or lacking in the hydrolysate. Injection of this mixture into dogs depleted by bleeding or starvation accelerated the restoration of plasma proteins. The nitrogen was retained, and nitrogen balance was restored. Presumably, the amino acids in the hydrolysate were utilized in the synthesis of new

[4] Addis, T., Poo, L. J., and Lew, W.: The quantities of protein lost by the various organs and tissues of the body during a fast, Jr. Biol. Chem., 1936, cxv, 111–116.

[5] Elman, R.: Intravenous injection of amino acids in regeneration of serum protein following severe experimental hemorrhage, Proc. Soc. Exper. Biol. and Med., 1937, xxxvi, 867–870.

protein, since administration of the incomplete hydrolysate (without addition of the two amino acids) did not raise the plasma protein, and the amino acids were not stored since the nitrogen was rapidly excreted.

More recently Elman and Weiner [6] reported the administration of this mixture by intravenous injection in several human cases of hypoproteinemia and edema. The edema was lessened or relieved; in most cases plasma proteins were increased, and nitrogen balance was restored. No appreciable reactions were observed. From the standpoint of practical therapeutics this procedure is obviously in the earliest experimental stage, but the results warrant the hope that it may eventually be established on a practical basis.

As expressed by Whipple et al.: [3] " Perhaps the most significant concept which derives from all these experiments is the fluidity of the body protein (including the plasma protein)—a ready give and take between the protein depots—a ' dynamic equilibrium ' of body protein."

P. W. C.

[6] ELMAN, R., and WEINER, D. O.: Intravenous alimentation, with special reference to protein (amino acid) metabolism, Jr. Am. Med. Assoc., 1939, cxii, 796–802.

REVIEWS

Carbon Monoxide Asphyxia. By CECIL K. DRINKER, M.D., D.Sc. 276 pages; 16 × 24 cm. Oxford University Press, London. 1938. Price, $4.50.

As a reference book for internists and a manual for industrial physicians, this book serves an excellent purpose. Carbon monoxide poisoning is frequent and as an acute emergency calls on the physician for prompt action based on accurate knowledge. Its sequelae are highly varied.

Few subjects have been better elucidated by research, and though many phases are still obscure, the physiologic and biochemical aspects, when presented as clearly as in this book, give to the reader a satisfying sense of complete understanding.

The monograph is written from a practical point of view and includes thorough discussion of the sources of carbon monoxide poisoning, statistical data, the problem of chronic exposure, the confusing subject of chronic poisoning and its effects, and a valuable chapter on treatment. In this last there is an account of the various methods of artificial respiration which is of great interest.

M. C. P.

The Therapeutics of Internal Diseases. Volumes I and II. Edited by GEORGE BLUMER, M.A., M.D.; Associate Editor, ALBERT J. SULLIVAN, M.D. Volume I: 872 pages; 25 × 17 cm. Volume II: 1042 pages; 25 × 17 cm. D. Appleton-Century Co., Inc., New York City. 1940. Price, $10.00 each volume.

These two volumes make up the first half of the projected set; the third and fourth volumes are to be published later in the current year. The publisher intends to present supplementary volumes in the future, at approximately $3.00 each, whenever advances or changes in therapeutic methods warrant additions to the work.

Volume 1 is general in its scope, including chapters on dietetics, climatology, spa therapy, physical therapeutic methods and their application, radiation therapy and occupational therapy. The chapter on the use of gases, by A. L. Barach, is especially interesting and helpful. Other chapters outline the general principles of endocrine treatment, the use of serums and vaccines, non-specific therapy, bacteriophage, and treatment in psychiatric problems.

The second section of this volume introduces special methods of therapeutic technic, oral and rectal medication, parenteral, intradermal, hypodermic, intramuscular and intravenous therapy, and ends with chapters on blood transfusion, spinal puncture, and paracentesis.

The first section of volume 2 (pages 3 to 458) is made up of two comprehensive chapters on pharmacology and toxicology by Louis S. Goodman. These chapters are interesting and well organized. Section 2 (pages 461 to 481) outlines some general principles of caring for the patient, including management of the convalescent and chronically ill. Section 3 (pages 485 to 969) takes up the management of the infectious diseases.

It is, of course, very difficult to present an accurate description of this comprehensive work in a brief review. Some adverse criticism might be suggested, particularly in reference to the lack of adequate cross editing of the different sections. For example the chapter on pneumonia, by Maxwell Finland, in volume 2, does not mention the discussion of the therapeutic use of gases by Barach, in volume 1, nor the article on the pharmacology of sulfapyridine in a different section of the same volume. Serum treatment of pneumonia is discussed in detail in volume 1, in the general article on serum therapy, and also in volume 2, in the chapter on pneumonia,

without cross reference. Certainly more complete editing would have better coordinated the efforts of the various authors, reduced the size of the volumes, and prevented repetition.

Opinion as to completeness must be deferred until the publication of volumes 3 and 4. Treatment of syphilitic infections of the central nervous system is not discussed in the chapter on syphilis; presumably it will be taken up in one of the two later volumes. The chapter on pulmonary tuberculosis omits discussion of the indications for phrenicotomy and thoracoplasty, and neglects entirely the erythrocyte sedimentation rate as a guide to treatment.

In general, however, there can be no doubt that "The Therapeutics of Internal Diseases" is a valuable publication, containing a wealth of useful and important information. The reviewer looks forward with anticipation to its completion in the near future.

T. N. C.

Brucellosis in Man and Animals. By I. Forest Huddleson, D.V.M., M.S., Ph.D., and contributing authors. 339 pages; 15.5 × 23.5 cm. Commonwealth Fund, New York. 1939. Price, $3.50.

Internists will find this excellent monograph very helpful. It is clearly written, definite in its statements, and covers the field very adequately.

The bacteriologic section will assist the clinical pathologist in improving the laboratory aids to diagnosis. At present in most hospitals, even of major size, attempts to cultivate Brucella are relatively perfunctory. The discussion of the serologic, allergic and opsonocytophagic tests includes material on methods and interpretation of great value to the internist. It may be noted in connection with cultural methods that no point is made of the danger of laboratory infections.

Clinical descriptions of the disease in humans are given separately for the American form, by A. V. Hardy, and for the disease as seen in Malta, by J. E. Debono. Both are excellent though it would appear that more detail might be helpful concerning certain aspects. In particular the localizations of Brucella in certain foci, though mentioned, are not discussed from the point of view of the variations in clinical course which are observed in such cases. The effects of removing a gallbladder infected with Brucella are occasionally dramatic.

Under differential diagnosis might have been included certain other puzzlingly similar conditions such as for example the Pel Ebstein type of fever in abdominal Hodgkin's disease.

There is a discussion of brucellosis in mammals which will be very informative to the medical reader.

The Commonwealth Fund greatly assists the profession by making it possible to obtain such a valuable monograph at a reasonable price.

M. C. P.

Convalescent Care: Proceedings of the Conference Held under the Auspices of the Committee on Public Health Relations of the New York Academy of Medicine. 261 pages; 16 × 23.5 cm. New York Academy of Medicine, New York. 1940.

Medical students often wonder at the system which devotes weeks of care in hospital to a decompensated heart case and discharges him to work for a living, suffer a relapse and return to the hospital. Graduate physicians have too often come to accept such illogical and wasteful use of medical facilities. However, today there is widespread interest in the development of chronic hospitals and of convalescent homes for the treatment of patients requiring institutional medical care of less elaborate nature but of greater length than can be given in the general hospital.

The proceedings of this well planned conference held in New York in 1939 are a major contribution to the relatively scant literature of convalescent care. The first session was devoted to general basic considerations, physiologic, psychologic, nutritional, etc. Then convalescent care for patients after various diseases was discussed. This group of papers contains many of great interest. The psychosomatic aspects of convalescence were presented at the third session and in the fourth the social, financial and administrative aspects of convalescent care were dealt with in six papers. The last session was given over to a summarization of the conference.

The book is stimulating reading to all internists and especially valuable to those who may be called on to assist their community in a wise development of its medical facilities.

M. C. P.

COLLEGE NEWS NOTES

Gifts to the College Library

Grateful acknowledgment is made of the receipt of the following reprints to the College Library of publications by members:

Dr. Walter H. Baer (Associate), Manteno, Ill.—1 reprint;
Dr. Nathan Blumberg, F.A.C.P., Philadelphia, Pa.—1 reprint;
Dr. Dwight T. Bonham (Associate), Hempstead, N. Y.—1 reprint;
Dr. J. Bailey Carter (Associate), Chicago, Ill.—3 reprints;
Dr. B. Earl Clarke, F.A.C.P., Providence, R. I.—1 reprint;
Dr. Joseph F. Elward (Associate), Washington, D. C.—1 reprint;
Dr. Samuel M. Feinberg, F.A.C.P., Chicago, Ill.—6 reprints;
Dr. Alvin G. Foord, F.A.C.P., Pasadena, Calif.—13 reprints;
Dr. Ernest E. Hadley, F.A.C.P., Washington, D. C.—1 reprint;
Dr. M. Coleman Harris, F.A.C.P., New York, N. Y.—1 reprint;
Dr. Charles E. Lyght, F.A.C.P., Northfield, Minn.—1 reprint;
Dr. Samuel Morrison, F.A.C.P., Baltimore, Md.—2 reprints;
Dr. Emma S. Moss (Associate), New Orleans, La.—7 reprints;
Dr. Frederick W. Mulsow, F.A.C.P., Cedar Rapids, Iowa—1 reprint;
Dr. Bruce R. Powers (Associate), Knoxville, Tenn.—1 reprint;
Dr. Harold L. Rakov (Associate), Kingston, N. Y.—1 reprint;
Dr. John C. Ruddock, F.A.C.P., Los Angeles, Calif.—3 reprints.
Lt. Col. Seymour C. Schwartz, F.A.C.P., (MC), U. S. Army—1 reprint;
Dr. John W. Shuman, Sr., F.A.C.P., Los Angeles, Calif.—1 reprint;
Dr. E. B. Winnett, F.A.C.P., Des Moines, Iowa—1 reprint.

Schedule of Examinations by Certifying Boards

The following Boards have announced schedules of their examinations as follows. For further details and application forms communicate with the respective secretaries.

American Board of Internal Medicine: William S. Middleton, M.D., Secretary 1301 University Avenue Madison, Wis.	Written Examination, October 21, 1940. Oral Examination, Philadelphia, December, 1940. Written Examination, February 17, 1941. Oral Examination, Boston, April, 1941, in connection with meeting of the American College of Physicians. Oral Examination, Cleveland, June, 1941, in connection with meeting of the American Medical Association.
American Board of Dermatology and Syphilology: C. Guy Lane, M.D., Secretary 416 Marlboro Street Boston, Mass.	Written Examination, October 28, 1940. Oral Examination, Chicago, December 6–7, 1940. Applicants in Group B take both the written and oral examinations; applicants in Group A take the oral examination only.
American Board of Psychiatry and Neurology: Walter Freeman, M.D., Secretary 1028 Connecticut Ave., N. W. Washington, D. C.	New York City, December 18–19, 1940.

AMERICAN BOARD OF RADIOLOGY: B. R. Kirklin, M.D., Secretary 102 Second Ave., S. W. Rochester, Minn.	Boston, September 26–29, 1940. Cleveland, June, 1941, at meeting of American Medical Association.
AMERICAN BOARD OF PATHOLOGY: F. W. Hartman, M.D. Secretary-Treasurer Henry Ford Hospital Detroit, Mich.	Cleveland, June, 1941 in connection with the meeting of the American Medical Association.

Dr. M. A. Ogden, F.A.C.P., has been appointed Director of Laboratories and Pathologist to the Passaic (N. J.) General Hospital.

The Golden Clinic, Elkins, W. Va., presented their sixth annual scientific program August 31. Dr. Pat Alexander Tuckwiller, F.A.C.P., Charleston, presided at a sectional luncheon of the West Virginia Heart Association and Dr. Staige Davis Blackford (Associate), Charlottesville, Va., presented a paper on "Present Concepts of the Therapy of Peptic Ulcer and Gall Bladder Disease" at this meeting.

Dr. L. J. Moorman, F.A.C.P., Oklahoma City, has been made President, Dr. Harold G. Trimble, F.A.C.P., Oakland, Calif., President-Elect, Dr. Victor F. Cullen, F.A.C.P., State Sanatorium, Md., Vice President and Dr. Benjamin L. Brock, F.A.C.P., Waverly Hills, Ky., Secretary-Treasurer of the American Trudeau Society.

Dr. Charles A. Doan, F.A.C.P., Columbus, was reëlected President and Dr. Henry Kennon Dunham, F.A.C.P., Cincinnati, was elected one of the Vice Presidents of the Ohio Public Health Association at its annual meeting in Cleveland, June 5.

Dr. Herbert R. Edwards, F.A.C.P., New York, was the guest speaker at this meeting, his subject being, "Revitalizing the Tuberculosis Control Problem."

Dr. Charles L. Brown, F.A.C.P., has been appointed Visiting Physician in the medical wards of the Philadelphia General Hospital, to succeed the late Dr. David Riesman, F.A.C.P.

Among the speakers at the annual meeting of the Rhode Island Medical Society in Providence in June were the following:

Dr. Robert F. Loeb, F.A.C.P., New York, "Adrenal Insufficiency and Its Present-Day Management";

Dr. Elliott P. Joslin, F.A.C.P., Boston, "Incidence of Diabetes in Rhode Island and Other States";

Dr. Clifton B. Leech, F.A.C.P., Providence, "Luetic Heart Disease in Rhode Island."

Dr. Ramón M. Suarez, F.A.C.P. and College Governor for Puerto Rico, San Juan, was one of the speakers at a recent meeting of the Mayaguez District Medical Society at Yauco, P. R. Dr. Suarez spoke on "Treatment of the Asthmatic Status."

Dr. Harry E. Ungerleider, F.A.C.P., New York, spoke on "Cardiac Arrhythmia" at a recent meeting of the American Life Convention in Colorado Springs.

Dr. Paul P. McCain, F.A.C.P., Sanatorium, N. C., was elected President and Dr. J. Burns Amberson, Jr., F.A.C.P., New York, one of the Vice Presidents of the National Tuberculosis Association at the annual meeting in Cleveland in June. Surgeon General Thomas Parran, F.A.C.P., U. S. Public Health Service, was made an Honorary Vice President of this organization.

Dr. Constantine F. Kemper, F.A.C.P., Denver, recently addressed the Northeast Colorado Medical Society on "Pernicious Anemia and Recent Advances in the Treatment of Ductless Gland Disorders."

Dr. Tomás Cajigas, F.A.C.P., Washington, was recently decorated with the Order of Carlos J. Finlay at a reception at the Cuban Embassy in Washington.

Dr. Robert M. Moore, F.A.C.P. and College Governor for Indiana, was the guest speaker at a recent meeting of the Gibson County (Ind.) Medical Society, Princeton, his subject being, "The Heart at Middle Age."

One of the annual Henry Russel awards at the University of Michigan, Ann Arbor, was recently given to Dr. Frank H. Bethell, F.A.C.P., Ann Arbor, for his "direction of field studies of anemias of pregnancy in Hillsdale County," in cooperation with the W. K. Kellogg Foundation.

Dr. Julius H. Hess, F.A.C.P., Chicago, discussed "Prematurity" and "Bronchiectasis in Childhood" at a symposium on Obstetrics and Pediatrics in Roaring Gap, N. C., June 16–17, held under the auspices of the State Board of Health and the postgraduate committee of the Medical Society of the State of North Carolina.

Dr. Harry L. Alexander, F.A.C.P., St. Louis, was one of the guest speakers at the annual spring clinic of the Providence (R. I.) Hospital Intern Alumni Association. Dr. Alexander presented a paper on "Physical Examination of the Patient, Stressing Emphysema."

Dr. Harold M. Coon, F.A.C.P., Statesan, Wis., and Dr. Frank L. Jennings, F.A.C.P., Indianapolis, Ind., were among those who spoke at a series of ten one-day institutes on diseases of the chest, under the sponsorship of the Wisconsin Anti-Tuberculosis Association, the committee on chest diseases of the state Medical Society of Wisconsin, the State Board of Health and the Wisconsin sanatoria.

Among the guest speakers at the recent annual meeting of the Wyoming State Medical Society, held in Sheridan, were the following:

Dr. Kenneth D. A. Allen, F.A.C.P., Denver, "Practical Considerations of Certain Diseases of the Cervix Uteri with Relation to Prevention of Cancer";

Dr. Peter T. Bohan, F.A.C.P., Kansas City, Mo., "Arthritis: Special Reference to Etiology and Management";

Dr. Charles Douglas Deeds (Associate), Denver, "Recent Advances in the Treatment of Heart Disease."

Dr. Oscar G. Costa-Mandry, F.A.C.P., San Juan, has been elected vice president of the General Anti-Tuberculosis Association of Puerto Rico.

Dr. Wingate M. Johnson, F.A.C.P., Winston-Salem, N. C., received the honorary degree of Doctor of Science at the recent commencement at Wake Forest College.

The Utah State Medical Association held its annual meeting in Ogden, August 29–31. Among the guest speakers at this meeting were the following:

Dr. James G. Carr, F.A.C.P., Chicago, "Obscure Fever; Clinical Diagnosis of Coronary Occlusion";

Dr. James F. Churchill, F.A.C.P., San Diego, "Diagnosis and Management of Heart Irregularities; Congestive Heart Failure."

Dr. Donald A. Palmer (Associate), Spokane, Wash., has been installed as President of the Pacific Northwest Medical Association.

Dr. Henry H. Turner, F.A.C.P., Oklahoma City, spoke on "Present Status of Endocrinology in General Practice" at the fifth Harlow Brooks Memorial Navajo Clinical Conference held at the Sage Memorial Hospital, Ganado, Ariz., August 26–28.

Under the auspices of the Iowa State Department of Health and the State University of Iowa College of Medicine, a three-day postgraduate course on the care of the newborn was held at the University Hospital, Iowa City. Among the lecturers were:

Dr. Julius H. Hess, F.A.C.P., Professor of Pediatrics, University of Illinois College of Medicine, Chicago;

Dr. Horton R. Casparis, F.A.C.P., Professor of Pediatrics, Vanderbilt University School of Medicine, Nashville.

Dr. Henry Kennon Dunham, F.A.C.P., Cincinnati, who recently retired as Medical Director of the Hamilton County (Ohio) Tuberculosis Sanatorium, was honored at a dinner given by the Christmas Seal Committee of Cincinnati and Hamilton County, of which he is President, the Cincinnati Anti-Tuberculosis League, the faculty of the University of Cincinnati College of Medicine and the staff of the Sanatorium.

Dr. Paul P. McCain, F.A.C.P., Sanatorium, N. C., was one of the speakers at the banquet.

Dr. Henry J. John, F.A.C.P., Cleveland, was one of the speakers on the scientific program at the meeting of the Tenth Councilor District of the Medical Society of the State of Pennsylvania in Pittsburgh, July 17.

Among the speakers at the scientific session of the fifty-first annual meeting of the Washington State Medical Association, held at Tacoma, Wash., August 25–28, were the following:

Dr. Kenneth K. Sherwood (Associate), Seattle, "Indications and Contraindications for Gold, Vitamin C, Sulfanilamide and Thiamine Therapy for Chronic Arthritis";

Dr. Edwin G. Bannick, F.A.C.P., Seattle, "Newer Procedures in the Treatment of Pneumonia";
Dr. Cassius H. Hofrichter, F.A.C.P., Seattle, "Clinical Evaluation of Standard Protamine Zinc and Crystalline Insulin."

The nineteenth annual meeting of the American Congress of Physical Therapy was held in Cleveland, September 2–6. Among the speakers at this meeting were:

Dr. Theodore G. Klumpp, F.A.C.P., chief of the drug division, U. S. Food and Drug Administration, "Application of the New Food, Drug and Cosmetic Act to Therapeutic Devices";
Dr. Edgar V. Allen, F.A.C.P., Rochester, Minn., "Treatment of Diseases of the Peripheral Blood Vessels";
Dr. Frank H. Krusen, F.A.C.P., Rochester, Minn., "Present Status of Ultraviolet Irradiation."

Dr. R. H. Sundberg, F.A.C.P., San Diego, has been elected President, Dr. Harold G. Trimble, F.A.C.P., Oakland, Vice President and Dr. E. Richmond Ware, F.A.C.P., Los Angeles, Secretary, of the California Tuberculosis Association.

The American Psychiatric Association held its first regional institute on post-graduate psychiatric education at the Agnew State Hospital, Agnew, Calif. Among those who participated in the institute were:

Dr. S. Spafford Ackerly, F.A.C.P., Professor of Psychiatry, University of Louisville School of Medicine, Louisville, Ky.;
Dr. Wendell S. Muncie (Associate), Associate Professor of Psychiatry, Johns Hopkins University School of Medicine, Baltimore, Md.;
Dr. Walter L. Treadway, F.A.C.P., Assistant Surgeon General, U. S. Public Health Service, now stationed at the University of California Medical School, San Francisco.

The Colorado State Medical Society held its seventieth annual session at Glenwood Springs, September 12–14. Among the speakers at this meeting were:

Dr. Nathan B. Van Etten, F.A.C.P., New York, President of the American Medical Association, "An American Health Program";
Dr. Tom Douglas Spies, F.A.C.P., Cincinnati, "Vitamin Therapy in Deficiency Diseases";
Dr. Charles Douglas Deeds (Associate), Denver, "Recent Advances in the Diagnosis and Treatment of Heart Disease."

Dr. John Walker Moore, F.A.C.P., Dean and Professor of Medicine at the University of Louisville School of Medicine, Louisville, Ky., received the honorary degree of Doctor of Science from Davidson College, Davidson, N. C.

Dr. Elliott P. Joslin, F.A.C.P., Clinical Professor of Medicine, Emeritus, Harvard University Medical School, Boston, received the honorary degree of Doctor of Science from Harvard University recently.

Dr. S. Bernard Wortis, F.A.C.P., New York, has been made Associate Professor of Neurology at New York University College of Medicine.

The sixty-sixth annual meeting of the Oregon State Medical Society was held in Eugene, Ore., September 4–7. Among the speakers at this meeting were:

Dr. Fred M. Smith, F.A.C.P., Iowa City, "Diagnosis and Treatment of Coronary Artery Disease; Cardiac Therapy; Prognosis and Treatment of Rheumatic Heart Disease";

Dr. Hans Lisser, F.A.C.P., San Francisco, "Indications for and Proper Use of Synthetic Male Hormone, Testosterone Propionate; Newer Synthetic Female Sex Hormone Preparations, Stilbestrol and Estradiol Dipropionate and Their Administration; Obesity and Leanness";

Dr. Blair Holcomb, F.A.C.P., Portland, "Education of the Diabetic Patient."

Dr. Homer P. Rush, F.A.C.P., Portland, was one of those who offered a symposium on "Fluid Administration by Parenteral Methods."

Under the sponsorship of the Department of Preventive Medicine, the Medical College of Virginia, Richmond, presented a two-day symposium on Industrial Health, September 12–13. Among the speakers were:

Dr. Bayard T. Horton, F.A.C.P., Rochester, Minn., "Peripheral Vascular Disease in Industry";

Dr. George H. Gehrmann, F.A.C.P., Wilmington, Del., "Objectives of Health Examinations and Their Industrial Applications."

Dr. D. G. Preston (Associate), Lewisburg, W. Va., was elected one of the Vice Presidents of the West Virginia State Medical Association at their meeting in White Sulphur Springs, July 29–31.

Postgraduate Facilities in Internal Medicine and Allied Subjects

The Board of Regents of the American College of Physicians has directed the publication in the "Annals of Internal Medicine," from time to time, of announcements relating to available educational opportunities in Internal Medicine and the allied specialties, particularly from the standpoint of postgraduate courses.

An attempt has been made, by communicating with the deans of all medical schools in the United States and Canada and with organized postgraduate meetings and societies, to collect all available data. Unfortunately the Executive Office has been unable to obtain replies from all these agencies, and, in some instances, when replies have been forwarded the information is somewhat incomplete. The following announcement of postgraduate courses and postgraduate meetings, therefore, will be supplemented in future reports. For greater detail, consult the institutions.

Part I—Graduate Institutions

Columbia University
New York Post-Graduate Medical School and Hospital
Irving S. Wright, M.D., Executive Officer
301 E. 20th Street
New York, N. Y.

Part-time Courses:

A number of courses in the field of medicine are offered three times during the year, beginning with the week of October 1, 1940, January 2, 1941 and April 1, 1941.

Courses consist of lectures and clinical demonstrations, stressing the diagnosis and treatment of the various disease conditions.

301—*Arthritis and Rheumatic Diseases*
Two months; 9:00 a.m. to 12:00 m., Tuesdays; Fee, $35.00.

303—*Cardiology*
Two months; 2:00 to 5:00 p.m., Mondays; Fee, $35.00.

304—*Clinical Interpretations of Laboratory Data*
Two months; 9:00 to 11:00 a.m., Wednesdays; Fee, $25.00.

307—*Diagnosis*
Two months; 9:00 a.m. to 12:00 m., Mondays; Fee, $35.00.

308—*Diseases of the Chest*
Two months; 9.00 a.m. to 12:00 m., Thursdays; Fee, $35.00.

309—*Diseases of the Thyroid and Other Endocrine Glands, and Obesity*
Two months; 9:00 a.m. to 12:00 m., Fridays; Fee, $35.00.

310—*Diseases of the Liver and Biliary Tract*
Two months; 11:00 a.m. to 1:00 p.m., Wednesdays; Fee, $25.00.

311—*Gastro-enterology*
Two months; 2:00 to 5:00 p.m., Wednesdays; Fee, $35.00.

312—*Clinical Hematology*
Two months; 3:00 to 4:00 p.m., Fridays; Fee, $15.00.

313—*Diabetes Mellitus and Nephritis*
Two months; 2:00 to 5:00 p.m., Thursdays; Fee, $35.00.

315—*Psychological Aspects of Internal Medicine*
Two months; 4:00 to 5:00 p.m., Fridays; Fee, $15.00.

318—*Pulmonary Tuberculosis*
Two months; 9:00 a.m. to 12:00 m., Saturdays; Fee, $35.00.

319—*Peripheral Vascular Diseases*
Two months; 2:00 to 4:00 p.m., Tuesdays; Fee, $25.00.

335—*Electrocardiography*
Two two-hour sessions weekly for four weeks; 9:00 to 11:00 a.m., Tuesdays and Thursdays; October 29–November 26, 1940, and April 1–24, 1941; Fee, $75.00.

344—*Advanced Electrocardiography*
Two two-hour sessions weekly for four weeks; 9:00 to 11:00 a.m., Tuesdays and Thursdays; December 3–26, 1940, and April 29–May 22, 1941; Fee, $100.00.

Full-time Courses

300—*Seminar in Internal Medicine*
Two months; Fee, $125.00 for one month; $200.00 for two months.

330—*Arthritis and Rheumatic Diseases*
Five days; September 30–October 4, 1940, and April 14–18, 1941; Fee, $35.00.

331—*Allergy*
Three weeks; December 2–20, 1940, and April 14–May 2, 1941; Fee, $150.00.

332—*Cardiovascular Diseases*
Four weeks; March 3–29, 1941; Fee, $125.00.

333—*Diseases of the Chest including Tuberculosis*
Ten days; October 21–November 1, 1940; Fee, $50.00.

334—*Endocrinology*
Ten days; October 7–18, 1940, and March 3–14, 1941; Fee, $50.00.

336—*Gastro-enterology*
Three weeks; September 9–28, 1940, and March 3–22, 1941; Fee, $75.00.

337—*Diabetes Mellitus, Nephritis and Hypertension*
Five days; November 11–17, 1940, and April 21–25, 1941; Fee, $35.00.

338—*Therapeutics*
Five days; December 2–6, 1940; Fee, $35.00.

340—*Peripheral Vascular Diseases*
Five days; December 9–13, 1940; Fee, $35.00.

341—*Symposium in Medicine*
Ten days; June 9–20, 1941; Fee, $30.00 for five days; $50.00 for ten days.

342—*Physical Diagnosis*
Ten days; January 13–24, 1941; Fee, $50.00.

345—*Electrocardiography*
Five days; October 14–18, 1940; Fee, $100.00.

347—*Clinical Interpretations of Laboratory Data*
Five days; June 2–6, 1941; Fee, $35.00.

348—*Tropical Medicine*
Five days; May 19–23, 1941; Fee, $50.00.

350—*Pulmonary Tuberculosis*
Four weeks; May 1–29, 1941; Fee, $100.00.

351—*Symposium on the Clinical Applications of Chemotherapy and Vitamins*
Five days; February 24–28, 1941; Fee, $35.00.

In addition to these part-time and full-time courses, the New York Post-Graduate Medical School has scheduled similar courses in neurology and psychiatry, pathology, pediatrics, bacteriology, dermatology and syphilology.

New York Polyclinic Medical School and Hospital
F. H. Dillingham, M.D., Medical Executive Officer
341–53 W. Fiftieth Street
New York, N. Y.

110—*Medicine*
Full-time Course; six weeks; integrated clinical and didactic study; fundamental theories applied in clinic; practical problems in diagnosis and treatment; demonstrations in medical specialties, including cardiology, allergy, arthritis, tuberculosis, diabetes and metabolism, gastro-enterology, pediatrics, neuropsychiatry and dermatology and syphilology.

The matriculant may supplement the course by an additional six weeks of actual work in the wards and outpatient department of the hospital.
Dates and fees not announced.

Pediatrics

This institution is prepared to offer two courses in this field, one in general pediatrics and one in endocrine diseases and disorders of infants, children and adolescents.
Dates of the courses and fees were not announced.

Dermatology and Syphilology

140—*Practical Instruction in Dermatology and Syphilology*
Six weeks; dates and fees not announced.

141—*Advanced Course in Dermatology and Syphilology*
Three months; dates and fees not announced.

142—*Syphilology*
Six weeks; dates and fees not announced.

Gastro-enterology
170—*Combined Course in Proctology, Gastro-enterology and Allied Subjects*
Six weeks; dates and fees not announced.

173—*Clinical Gastro-enterology, for the General Practitioner*
Six weeks; dates and fees not announced.

Neuropsychiatry
A general course is announced, though dates and fees are not given.

Pathology and Bacteriology
182—*Blood Transfusions*
A short course; dates and fees not announced.

Roentgenology
190—*Practical Roentgenological Interpretation and Technic*
Three months, or shorter courses by special arrangement; dates and fees not announced.

University of Pennsylvania Graduate School of Medicine
George H. Meeker, Ph.D., Dean
36th & Pine Streets
Philadelphia, Pa.

This institution does not schedule short intensive courses, but offers basic study courses in the major clinical departments. A fee of $800.00 is required for the basic studies in any one of the major clinical departments. There are no fees for continuation studies leading to the Master's and Doctor's degrees for candidates who have previously paid fees for underlying basic clinical studies. When the Master's degree is conferred, for continuation clinical and thesis studies, there is a graduation fee of $100.00. All the following basic study courses require eight months and are given from October to June annually: internal medicine, pediatrics, neurology-psychiatry, dermatology-syphilology, radiology.

The Graduate School of the University of Pennsylvania also sponsors "personal courses," designed to furnish to physicians relatively brief opportunities for mis-

cellaneous studies in subdepartmental subjects. Academic credits are not involved. Fees for personal courses are arbitrary, and are not affected by the total hours, or time periods, involved in actual work.

TABULATION OF PERSONAL COURSES

Cardiology—William D. Stroud, M.D., Professor of Cardiology.
8 Thursdays, 52 hours, courses beginning the first Thursday of October, January and April; Fee, $80.00.

Parasitology and Tropical Medicine—Damaso deRivas, M.D., Professor of Parasitology.
6 weeks, 150 hours; Fee, $125.00.

Clinical Gastro-enterology—H. L. Bockus, M.D., Professor of Gastro-enterology.
16 weeks, 500 hours; Fee, $400.00.

Allergy—H. B. Wilmer, M.D., Associate Professor of Allergy.
4 weeks, 40 hours; Fee, $150.00.

Diabetes Mellitus—Edward S. Dillon, M.D., Assistant Professor of Diseases of Metabolism.
2 to 4 weeks, 75 hours; Fee, $150.00.

Clinical Psychiatry—S. DeW. Ludlum, M.D., Professor of Psychiatry.
8 weeks, 240 hours; Fee, $160.00.

Clinico-biologic Neurology and Psychiatry—D. W. Bronk, Ph.D., Professor of Neurology; Earl D. Bond, M.D., Professor of Psychiatry; and Associates.
10 weeks, 250 hours; Fee, $100.00.

Part II—Other Medical Colleges

Boston University School of Medicine
Alexander Begg, M.D., Dean
750 Harrison Ave.
Boston, Mass.

Boston University School of Medicine offers the following courses in cardiac diagnosis:

Clinical Electrocardiography—James M. Faulkner, M.D.

Cardiac Roentgenology—George Levene, M.D.

Teaching clinics will be held at the Massachusetts Memorial Hospitals and will consist of twelve sessions of two hours each on Wednesdays from 10:30 a.m. to 12:30 p.m. from October 2 to December 18. Fee, $50.00 for one course; $75.00 for both courses.

Johns Hopkins University School of Medicine
Alan M. Chesney, M.D., Dean
710 N. Washington St.
Baltimore, Md.

No specific schedule of formal graduate courses is offered. However, the School of Medicine offers to a limited number of graduates in medicine opportunities for study in the various departments. Candidates desiring to avail themselves of these

opportunities must be acceptable to the heads of the departments in which they wish to work; qualified candidates must enroll for periods of three academic quarters of two months each as a minimum, and preferably for a complete academic year; these opportunities for study are chiefly in the clinical departments, where the graduates will assist in the care of outpatients, doing a certain amount of laboratory study and occasionally undertaking an investigation in the history rooms or in the clinics and laboratories; courses of study are largely individualized, according to needs of candidate; fee, $50.00 each academic quarter.

New York Medical College
Claude A. Burrett, M.D., Dean
5th Ave. at 105th St.
New York, N. Y.

Plan A:

Opportunities for systematic training, leading to a graduate degree and extending over a period of three years, are offered to approved physicians who wish to qualify for practice in such clinical specialties as medicine, pediatrics, radiology and other branches; in order to qualify for a graduate degree candidates must satisfactorily complete three sessions or periods of study, each of approximately a year's duration—one year as a non-resident fellow devoted to theory and fundamentals, and two years in clinical practice and research as a hospital resident; candidates must pass oral and written examinations and satisfy all other requirements, including the completion of a research problem.

The bulletin outlines specific courses leading to the degree of Master of Science in Medicine in *Internal Medicine, Pediatrics* and *Radiology,* as well as some of the surgical specialties. The education committee is convinced that those who successfully complete these courses will be prepared for examination by the various American Specialty Boards.

Matriculation fee, $10.00; tuition fee, first session, $400.00; no fee when in residency; graduation fee, $35.00.

Plan B:

Short courses by various College and Hospital departments to provide opportunities for practicing physicians to become familiar with new methods and technics; not credited toward a degree.

Electrocardiography—David Scherf, M.D., in charge.
Twenty conferences; December 16 to 31, 1940, and June 16 to 30, 1941; fee, $100.00.

Clinical Cardiology—David Scherf, M.D., in charge.
Twenty conferences; December 16 to 31, 1940, and June 16 to 30, 1941; fee, $100.00.

Tuberculosis—George Ornstein, M.D., and Staff.
May 1–31, 1941; fee, $100.00.

Physical Diagnosis—Herbert Elias, M.D., in charge.
Twenty conferences; December 16 to 31, 1940, and June 16 to 30, 1941; fee, $100.00.

Clinical Hematology—Louis Greenwald, M.D., in charge.
Twenty conferences; December 16 to 31, 1940, and June 16 to 30, 1941; fee, $100.00.

Management of the Diabetic—Thomas H. McGavack, M.D., in charge.
Twenty conferences; December 16 to 31, 1940, and June 16 to 30, 1941; fee, $100.00.

Endocrinology—Thomas H. McGavack, M.D., in charge.
Twenty conferences; December 16 to 31, 1940, and June 16 to 30, 1941; fee, $100.00.

All courses given at New York Medical College and Metropolitan Hospital, except Tuberculosis, which will be given at Metropolitan and Sea View Hospitals.

New York University College of Medicine
Currier McEwen, M.D., Dean
477 1st Ave.
New York, N. Y.

Graduate Study of Medicine—three-year full-time course.
A limited number of recent graduates in medicine who have had at least two years' interneship or its equivalent will be admitted to this course in internal medicine; problems pertaining to the basic medical sciences as applied to clinical medicine are developed by the students under the guidance of a member of the faculty and in conjunction with other departments, according to the nature of the study; fee, $12.00 for each year of work.

Short Courses

Internal Medicine
Five mornings per week for a period of one month; each month constitutes a complete session; eight sessions during the year, from October through May; fee, per session, $50.00.
Course designed for physicians in general practice desiring a practical review of recent advances in diagnosis and treatment; instruction will be given to small groups.

Clinical Electrocardiography
Fifteen weeks, 2:30 to 4:30 p.m., Mondays; October 7, 1940–January 13, 1941, and February 3–May 12, 1941; fee, per session, $50.00.
Interpretation of the electrocardiogram and its practical application; measurement and analysis of a large number of curves; operation of standard instruments; normal and abnormal electrocardiograms; Louis F. Bishop, Jr., M.D., Director; courses given by the Fourth Medical Division of Bellevue Hospital.

Northwestern University
J. Roscoe Miller, M.D., Director of Courses
303 E. Chicago Ave.
Chicago, Ill.

This institution conducts postgraduate courses in gastro-enterology, cardio-renal-vascular medicine, endocrinology and hematology by short intensive courses of from six to twelve days, with fee of $25.00 for one-week courses and fee of $50.00 for two-week courses; late August and early September schedule already completed; no announcement at hand for repetition of these courses later in year.

Stanford University School of Medicine
L. R. Chandler, M.D., Dean
2398 Sacramento St.
San Francisco, Calif.

This institution conducts postgraduate medical courses for practicing physicians in coöperation with the San Francisco Department of Public Health and the San Francisco Hospital; courses of one-week duration are given each year and those for 1940 have already been completed; bulletin listed pediatrics, gastro-enterology, management of hypertension and nephritis, roentgen-ray diagnosis and therapy.

Tufts College Medical School, Postgraduate Division
Samuel Proger, M.D., Chairman
30 Bennet St.
Boston, Mass.

This institution will offer the following courses during the fall of 1940. In addition to the tuition fee noted under each course, there is a $5.00 registration fee. This fee covers all courses taken within a twelve-month period.

Electrocardiography—September 16–21.

To familiarize the general practitioner, through demonstrations and intensive study of records, with the present status of electrocardiogram interpretation. An advanced course will be given in January for those who have satisfactorily completed this course. Dr. Heinz Magendantz in charge. Fee, $25.00.

Hematology A—October 21–26.

Mornings are spent at staff conferences and on laboratory and clinic work in the Joseph H. Pratt Diagnostic Hospital and Boston Dispensary. In the afternoons there are case presentations and lectures on the following subjects: bone marrow; anemia (pernicious, iron deficiency, and hemolytic); leukopenic disorders; leukemia. Dr. Heinrich G. Brugsch and Dr. William Dameshek in charge. Fee, $25.00.

Allergy—October 28–November 2.

The course is intended, through clinic demonstrations and lectures, to familiarize the general practitioner with the present-day status of the diagnosis and treatment of allergic conditions. Dr. Ethan Allan Brown in charge. Fee, $25.00.

Diseases of the Chest—October 28–November 2.

Teaching ward rounds and clinics will be held at the Corey Hill and Deaconess Hospitals, the Norfolk County Sanatorium, and the Boston Dispensary. Lectures and demonstrations will be given in the Joseph H. Pratt Diagnostic Hospital. Dr. Richard H. Overholt in charge. Fee, $25.00.

Radiology—November 11–16.

The course is intended to familiarize the general practitioner with the fundamentals of x-ray interpretation. The attempt is made to consider all the systems of the body in the study of which x-ray is of prime importance. Dr. Alice Ettinger in charge. Fee, $25.00.

Cardiology—November 25–30.

The course will emphasize the practical application of present-day knowledge of heart disease. Throughout the course therapy of heart disorders will receive especial attention. Dr. Samuel Proger in charge. Fee, $25.00.

Gastro-enterology—December 2–7.

This course is designed to familiarize the general practitioner with modern methods of examination of the gastro-intestinal tract, as well as with the diagnosis and treatment of gastro-intestinal disease. The clinical and laboratory facilities of the Boston Dispensary and the Joseph H. Pratt Diagnostic Hospital furnish ample material for demonstration and informal discussion. Dr. Katherine S. Andrews in charge. Fee, $25.00.

Tulane University of Louisiana School of Medicine
Maxwell E. Lapham, M.D., Dean
1430 Tulane Ave.
New Orleans, La.

Annual Clinic Week, October 7–12, 1940

Registration fee, $5.00.

Open to all licensed practitioners of medicine; consists of all-day lectures, demonstrations and day clinics, covering the entire field of medicine and its branches.

Review Courses

Review courses are designed largely for general practitioners, but offer a rather comprehensive review for anyone who has been unable to keep abreast of the literature.

The Medical Review Course

Four weeks, January 6 to February 1, 1941; fee, $100.00.

Course in medicine includes pediatrics and some radiological interpretation.

Tropical Medicine and Parasitology

September 30, 1940, to February 7, 1941; course designed to equip physicians for the practice of medicine in the tropics.

Throughout the year Tulane University arranges on demand part-time intensive instruction in certain subjects such as cardiology, pediatrics, cystoscopy, etc.

University of Arkansas School of Medicine
Stuart P. Cromer, M.D., Dean
Little Rock, Ark.

The postgraduate committee of the Arkansas State Medical Society, in connection with the University, will give a two-day general postgraduate course in Little Rock October 16–17, 1940; internal medicine will not be featured exclusively, but there will be some refresher courses offered in physical diagnosis and other subjects in the field of internal medicine.

University of Buffalo School of Medicine
Edward W. Koch, M.D., Dean
24 High St.
Buffalo, N. Y.

20th Annual Session—Course for general practitioners

September 16–28, 1940.

A course designed to acquaint general practitioners with the advances brought forth each year in medicine, surgery, obstetrics and the specialties; review of fundamental subjects in connection with clinical problems; designed to

meet the requirements of the active physician in general practice and to avoid the discussion of the subjects in a highly specialized manner; round table discussions; therapeutics; bedside instruction; fee, $50.00.

University of California Medical School
M. S. Marshall, M.D., Acting Dean
San Francisco, Calif.

Dermatology

January 6–8, 1941; fee, $20.00; an intensive refresher course on the clinical aspects of dermatology; given at the University of California Hospital.

In June, 1941, another refresher course will be given, but subject and announcements referring thereto will come later.

University of Chicago, Division of the Biological Sciences
c/o Dean of Students, Biological Division
Chicago, Ill.

1. Advanced Gastroscopy

Course given under supervision of Dr. Schindler; limited to one student per College quarter; course offered during the summer, autumn and winter quarters; fee, $150.00.

2. Gastroscopy

Two weeks, repeated each month at definite periods; fee, $100.00; course under direction of Dr. Schindler; registration limited to three physicians; applicants requested to indicate on their applications what special preparation or experience they have had in this field; arrangements for the course usually should be made many months in advance.

University of Georgia School of Medicine
G. Lombard Kelly, M.D., Dean
Augusta, Ga.

By special arrangement with the Head of the Department of Medicine, the University of Georgia School of Medicine will receive for training a limited number of physicians who may desire postgraduate training in internal medicine. Arrangements for such training may be made with the Professor of Medicine.

University of Illinois
1853 W. Polk St.
Chicago, Ill.

This institution offers no short intensive courses in internal medicine, but does offer graduate work leading to the Master's Degree in Medicine, based on research and advanced study; further details to be secured from the Recorder.

University of Michigan Medical School
A. C. Furstenberg, M.D., Dean
Ann Arbor, Mich.

The Department of Postgraduate Medicine of the University of Michigan announces the following annual postgraduate courses for the spring of 1941:

Allergy

Course in clinical phases of allergy offered to a limited group; taught mainly by demonstrations; includes study of asthma, hay fever, food allergy, eczema, contact dermatitis and dust sensitization, with methods of recognition and treatment. The practical aspects and office management of these conditions are emphasized. The course is arranged so that the entire field of allergy can be presented over a period of successive years. One week; fee, $10.00.

Diseases of Blood and Blood-Forming Organs

Course consists of a comprehensive review of the present knowledge of the blood, its physiology, embryology, and pathology. Clinical and laboratory studies are made of a selected group of patients. Standard laboratory methods are demonstrated and analyzed, and special features, as bone-marrow puncture, blood transfusion, etc., are considered. The course is planned to enable the physician to obtain a better understanding of the status of blood-forming organs and to select the most adequate treatment for his patients. One week; fee, $7.50.

Diseases of the Heart

Clinical aspects of heart disease are stressed in this short intensive course. Instruction includes examination of patients and practical demonstrations of cases. References for study in advance of the course are suggested. Three days; fee, $5.00.

Electrocardiographic Diagnosis

This course consists of lectures with lantern slides and demonstrations, and the examination under supervision of a large number of electrocardiograms from the files of the laboratory. One week; fee, $25.00.

Nutritional and Endocrine Problems

This course is planned to acquaint the practitioner with the fundamental principles of metabolism. The phenomenal advances in biological chemistry and clinical investigation have gone far to explain a number of disease conditions which either have not been understood or for which there was no satisfactory treatment. These conditions include diabetes mellitus, nephritis and edema, obesity, deficiency diseases, gout, and dysfunctions of the parathyroid and the adrenal glands. Material will be presented by means of lectures, demonstrations, and selected reading. One week; fee, $7.50.

Pathology

Four intensive courses, especially arranged for postgraduate students, are offered during the summer session. These courses are as follows:

Special Pathology of Neoplasms: Histopathological diagnosis of neoplasms with special emphasis on rare forms. Discussion on diagnosis, treatment, and prognosis. Laboratory open all day. Demonstration, 3–5 p.m. daily. Two weeks; fee, $15.00.

Pathology of the Female Genito-Urinary Organs: This course deals with the microscopical pathology of the female genito-urinary tract, with special emphasis upon neoplasms of both external and internal genitalia. The more important infections are illustrated in their various situations and special attention is paid to the interpretation of endometrial curettings. Laboratory open all day. Demonstration 3–5 p.m. daily. Two weeks; fee, $15.00.

Special Pathology of the Eye: Laboratory open all day. Demonstration, 3–5 p.m. daily. Two weeks; fee, $15.00.

Special Pathology of the Ear, Nose, and Throat: Laboratory open all day. Demonstration, 3–5 p.m. daily. Two weeks; fee, $15.00.

Pediatrics

This course, contributed by the American Academy of Pediatrics, consists of lectures and clinics on those conditions in infancy and childhood which contribute prominently to mortality and disability. Three days; no registration fee.

Diagnostic Roentgenology. III. The Skeletal System including the Skull

This is the third in a series of courses in diagnostic roentgenology. This course will be limited in scope to roentgen consideration of the skeletal system including the skull. No instruction in roentgen technic will be offered. One week; fee, $10.00.

Internal Medicine—Courses designed to prepare candidates for national specialty board examinations.

Courses are arranged in internal medicine and most of its subdivisions for indeterminate periods for those desiring special training. While exceptions may be made, these courses are primarily designed for those who have had the preliminary training required by the national specialty boards. Each course is arranged individually to take advantage of the large amount of pathological material, the anatomical and chemical laboratories, as well as the special departments in hematology, arthritis, serology and psychiatry. Fee, $25.00 per month.

The program of this institution also calls for a number of postgraduate courses to be given during the summer of 1941, including courses in biological chemistry, dermatology and syphilology, internal medicine, clinical microscopy, neurology, pathology, autopsies, and medical roentgenology.

University of Virginia
H. E. Jordan, M.D., Dean
University, Va.

Postgraduate Clinics

During the session this University gives two postgraduate clinics, one in the autumn and one in the spring; these clinics are designed primarily for the practitioners of the State; specific dates not given; no registration fee.

Recent Advances in Internal Medicine

The above course was given June 17 to 22, 1940, and the intention has been expressed of giving the course again during June, 1941; fee, $15.00.

University of Wisconsin Medical School
William S. Middleton, M.D., Dean
Madison, Wis.

In addition to the opportunities in residencies and research fellowships, the University of Wisconsin Medical School has made the following announcement:

Observation courses have been organized by the Medical Faculty and Staff of the State of Wisconsin General Hospital upon the approval of the Regents of the University of Wisconsin. No stereotyped courses or lectures are afforded, but attendance upon lectures, clinical services and staff meetings of the Hospital is arranged. A stated fee is charged all physicians in attendance upon the clinical services for periods exceeding one (1) month. This fee shall be $100.00 per month or $400.00 per semester and shall be credited to the department to which the physician is assigned. A certificate of attendance shall be granted upon the completion of the course and shall be signed by the President, Dean of the Medical School and chief of the responsible department. No credit toward an advanced degree may be earned

by such attendance, nor is it purposed to include the existing residencies in the scope of this recommendation.

Vanderbilt University School of Medicine
John B. Youmans, M.D., Department of Medicine
Nashville, Tenn.

1. Medicine

These courses, which are designed primarily for the holders of Commonwealth Fund fellowships, are given during the summer from approximately mid-June to mid-July. The course is of one month's duration and consists of seminars, conferences and practice work in the wards and the outpatient department in Internal Medicine and allied specialties of dermatology, neurology, psychiatry, metabolic diseases, allergy, diseases of the chest and syphilis.

It is designed to review this field for the general practitioner and acquaint him with the advances in diagnosis and treatment. A limited number of physicians in addition to the holders of Commonwealth Fund fellowships will be accepted under certain conditions. Tuition, $50.00.

2. Syphilis—Medicine 12. For County Health Officers and Physicians with Appointment in Public Health Units

This course is open to county health officers and physicians with appointments in public health units. It is designed to familiarize the health officer with all aspects of the syphilis problem. It offers him the opportunity of studying the individual patient, history taking, physical examination, darkfield and lumbar puncture procedures and treatment.

The student attends each clinic session for a period of four weeks and assists in the conduct of the clinic. A series of lectures early in the course is given to review the clinical and epidemiological aspects of syphilis. The remainder of the time is devoted to field work, under the direction of the epidemiologist. Several such courses are given from September to April inclusive. Each course is limited to six physicians. No tuition fee.

3. Syphilis—Medicine 13. Postgraduate Course in Syphilis

This course is open to properly qualified physicians wishing to secure special training in syphilis. It is designed to offer training fitting the student for positions of responsibility in syphilis control work.

The physician is expected to take his place as one of the staff of the clinic, to examine and treat his patients, assuming responsibility for them. Opportunity for thorough training is offered in the conduct of a syphilis clinic, the diagnosis of the disease, including darkfield and lumbar puncture procedures and in treatment. Epidemiological field work is to be done under the direction of the epidemiologist of the syphilis clinic.

Physicians will be accepted for such work for a period of six to twelve months, dependent upon the needs of the individual physician. No tuition fee.

4. Syphilis B. Demonstration in Syphilis Clinic Management for Physicians and Nurses

This course is open to physicians and registered nurses. It is designed to give an opportunity to physicians and nurses to observe the management of patients and clinic procedures for a period of two weeks at intervals during the year. Several such courses are given from September to April inclusive. No more than three physicians and two nurses will be accepted during each period. No tuition fee.

5. Graduate Course in Internal Medicine

This course consists of supervised work with patients in the medical outpatient service, including the related specialties; experience in the diagnostic laboratories; assigned reading, seminars and conferences, including pathological and radiological conferences and autopsy study; directed study and seminars in the pre-clinical sciences, particularly physiology and biochemistry. Special investigation of a particular problem in one of the divisions of internal medicine as the basis of a thesis is required. The course extends over a period of one year and is open to physicians who have completed an internship, have had an additional year's experience as assistant resident in medicine or its equivalent and are acceptable to the school. Courses begin July 1 and are limited to six students. Tuition fee, $300.00.

Fellowships

Three fellowships are available for this course described above. These fellowships, which provide tuition, board and lodging, are open to those who meet the requirements mentioned above and will be awarded on the basis of the individual's training and recommendations.

6. Special work in the Department of Medicine may be made available by special arrangement.

Tuition and fees according to arrangement.

Further information regarding these courses should be addressed to the Registrar of the School of Medicine, Vanderbilt University, Nashville, Tenn.

Women's Medical College of Pennsylvania
Dr. Margaret D. Craighill, Acting Dean
Henry Ave. & Abbottsford Rd.
East Falls, Philadelphia, Pa.

This institution offers but one postgraduate course. This is an intensive course of two weeks' duration in electrocardiographic technic given during the summer months, if five registrants are obtained. Fee, $100.00.

Yale University School of Medicine
333 Cedar St.
New Haven, Conn.

Any physician of good standing in the community may on application to the head of a department in the Yale University School of Medicine obtain permission to attend clinics, lectures, conferences or ward rounds; or to do special work in association with the laboratories connected with the various departments. The institution lists opportunities for observation in medicine, pediatrics, psychiatry, pathology, public health, child development and the surgical specialties, giving hours of ward rounds, staff conferences, seminars, demonstrations, etc. There are no formally organized postgraduate courses announced.

Part III—Postgraduate and Clinical Meetings

The American College of Physicians
4200 Pine St.
Philadelphia, Pa.

A group of one and two week intensive postgraduate courses will be scheduled immediately preceding the Annual Session of the College at Boston, April 21–25, 1941.

The Committee on Postgraduate Education, headed by Dr. Edward L. Bortz of Philadelphia, has announced that courses in advanced internal medicine, cardiology, hematology and other associated branches will be given in four or five different centers of the United States during the period April 7–19, 1941. Bulletins and detailed announcements will be issued later.

The Twenty-Fifth Annual Session of the College, covering internal medicine and its allied specialties and consisting of General Sessions, Special Lectures, Panel Discussions, Clinics and Demonstrations, will be held in Boston, April 21–25, 1941, with headquarters at the Statler Hotel.

Dallas Southern Clinical Society
1133 Medical Arts Bldg.
Dallas, Texas

The Dallas Southern Clinical Society will hold its 13th Annual Spring Clinical Conference in Dallas at the Hotel Adolphus, March 17–20, 1941. The meeting will consist of general assemblies, postgraduate teaching, clinics, round tables, clinical-pathological conferences, and scientific and technical exhibits. Among the guest speakers in the specialties indicated will be the following:

Dr. C. J. Barborka, Chicago .....Medicine
Dr. W. Edw. Chamberlain, Philadelphia .....Radiology
Dr. Harry Goldblatt, Cleveland .....Pathology
Dr. Henry G. Poncher, Chicago .....Pediatrics
Dr. Marion B. Sulzberger, New York .....Dermatology
Dr. Soma Weiss, Boston .....Medicine

These speakers will appear daily in general assemblies, clinics, and symposia. In addition, local members of the profession will present a series of postgraduate lectures and one afternoon of clinics and symposia.

Any physician who is a member of his county medical society may register. Registration fee, $10.00.

The New York Academy of Medicine
2 East 103rd Street
New York, N. Y.

The 1940 Graduate Fortnight will be held October 14 to 25, 1940. The subject will be "Infections." The program will consist of morning panel discussions, afternoon hospital clinics, evening addresses, scientific exhibits and demonstrations. Registration limited to the medical profession; Fellows of the Academy admitted without fee; all others pay registration fee of $5.00.

Oklahoma City Clinical Society
609 Medical Arts Bldg.
Oklahoma City, Okla.

The 10th Annual Fall Clinical Conference of the Oklahoma City Clinical Society will be held in Oklahoma City at the Biltmore Hotel, October 28–31, 1940. The meeting will consist of general assemblies, postgraduate symposia, round table discussions, and clinics. The program will include many guest speakers from various parts of the country, who are prominent in their own specialties. Registration fee, $10.00.

Omaha Mid-West Clinical Society
1036 Medical Arts Bldg.
Omaha, Nebr.

The 8th Annual Assembly of the Omaha Mid-West Clinical Society will be held in Omaha, Nebr., at the Paxton Hotel, October 28 to November 1, 1940.

This society is made up of one hundred and twenty-five active members, all located in Omaha and all members of the faculty of the medical school of either Creighton University or Nebraska University. The membership is divided into sections according to specialties. Among the sections are medicine, pediatrics, neuropsychiatry, radiology, dermatology, and the basic sciences. This Assembly will offer five days of intensive graduate study presented by a distinguished group of from fifteen to seventeen guest speakers. Each will give two addresses and one clinic. One day of the meeting will be devoted to a symposium on the anemias, discussed by Drs. Frank H. Bethell, Ann Arbor, Mich.; George M. Curtis, Columbus, Ohio; Willis M. Fowler, Iowa City, Iowa; Frank J. Heck, Rochester, Minn.; and Roy R. Kracke, Decatur, Ga. A local lecture program will be presented by forty-eight active members of the society. Annual dues of active members, $10.00; $5.00 registration fee paid by all attending the Assembly.

Philadelphia County Medical Society
21st & Spruce Sts.
Philadelphia, Pa.

The 6th Annual Postgraduate Institute of the Philadelphia County Medical Society, under the direction of Rufus S. Reeves, M.D., will be held in Philadelphia at the Bellevue-Stratford Hotel, March 31 to April 4, 1941. The subject of this Postgraduate Institute will be "Symposia on Modern Therapy," and will cover immunology, pediatrics, dermatology, gastroenterology, physiotherapy, allergy, chemotherapy, the avitaminoses, x-ray therapy, pneumonia and upper respiratory infections, the acute infections, and gynecology. The program will be made up of speakers whose work is authoritative, who are members of the various medical schools, and who are members of the Philadelphia County Medical Society.

All members of a county medical society in good standing are eligible for registration. Fee, $5.00.

OBITUARIES

DR. STUART PRITCHARD

Stuart Pritchard, M.D., F.A.C.P., aged 58 years, died at his home in Battle Creek, Mich., at 4:45 p.m., Sunday, August 4, 1940. Dr. Pritchard became ill about six months previously. The first indication of his illness manifested itself by a rapid enlargement of the thyroid gland while he and Mrs. Pritchard were spending their vacation at their winter home in Barbados, British West Indies. Sensing the necessity of early medical skill, he came by air to the University Hospital at Ann Arbor, Mich. On April 16 an operation was performed and it was discovered that the enlargement was due to sarcoma of the thyroid, the gravity of which was immediately recognized. Every possible aid that medical and surgical science had to offer was secured, but the disease rapidly progressed until his death.

Dr. Pritchard was born at Auburn, Ont., Canada, in 1882. He secured his degree of Doctor of Medicine from the University of Toronto Faculty of Medicine in 1905. He was one of twelve prominent Americans awarded honorary degrees at the 96th commencement of the University of Michigan last June. At that time the degree of Doctor of Science in Medicine was conferred upon him for "distinguished and outstanding contributions to the field of Medicine and Public Health."

Dr. Pritchard was frequently appointed to positions of responsibility. Last November he participated, by order of the Secretary of State, in an educational conference in Washington, being among two hundred representatives of twenty-one American Republics.

After his graduation in medicine, Dr. Pritchard spent several years associated with Dr. Parfitt at Gravenhurst, Ont., and later with Dr. VonRuck at Asheville, N. C., in the study and treatment of tuberculosis. Soon after this, in 1917, Dr. Pritchard joined the staff of the Battle Creek Sanitarium as Chief of the Chest Department, where he remained in active service for seventeen years. During this period he spent considerable time in presenting papers before medical societies throughout this country and Canada, and gained a national and international reputation as an authority on pulmonary diseases.

In 1928 Dr. Pritchard represented the United States Government at an international conference on tuberculosis at Rome, Italy; and in 1932 he was delegated by the President as the nation's delegate to the Hague Conference of the International Union Against Tuberculosis.

He was honored by the presidency of the leading tuberculosis societies of the nation—the National Tuberculosis Association, the Mississippi Valley Tuberculosis Association, and the Michigan Trudeau Society, of which he was one of the founders.

He was a Fellow of the American College of Physicians and American Medical Association, a member of the International Union Against Tuberculosis, the American Climatological Association, the American Association of Thoracic Surgery, the Society of Thoracic Surgeons, the Mississippi Valley Tuberculosis Association, the Radiological Society of North America, the American Public Health Association, the Michigan State Medical Society, and the Michigan Trudeau Society.

Dr. Pritchard had unusual organizing ability which was recognized by Mr. W. K. Kellogg who chose Dr. Pritchard as head of the W. K. Kellogg Foundation, which position he held to the time of his death. Under Dr. Pritchard's guidance the Foundation established health departments in seven counties; it also assisted schools in these same counties. It provided tuition in universities and psychiatric clinics for groups of teachers, supervisors, school board members, ministers, newspaper editors, physicians, nurses, dentists and veterinarians.

Dr. Pritchard recognized that a policy of patronage would fail where a program of participation and coöperation would succeed; as a result the Foundation is doing a remarkable work.

CHARLES E. STEWART, M.D., F.A.C.P.

DR. JOHN A. LANFORD

Dr. John A Lanford, F.A.C.P., of New Orleans, La., who was born in Gainesville, Ala., June 19, 1881, died July 2, 1940.

In the passing of Dr. Lanford, the medical profession of Louisiana has lost one of its most distinguished members and the College has suffered an irreparable loss.

In the Louisiana State Medical Society, he rendered most valued service as a member of the Journal Committee, which shapes and controls the policies of the official journal of the Society.

As Chairman of the Cancer Committee of the Louisiana State Medical Society since 1932, he accomplished much in the way of enlisting the members of the profession in the work of cancer control, as well as educating the public regarding what everybody should know about cancer.

He was educated in his native state, receiving a Ph.G. degree from Alabama Polytechnic Institute in 1900, and his M.D. degree from the University of Alabama School of Medicine in 1905. From 1908 to 1910 he was Instructor of Anatomy at the University of Alabama School of Medicine; from 1911 to 1914 he was Instructor of Surgical Pathology, and since 1914, Assistant Professor of Pathology and Bacteriology at Tulane University of Louisiana School of Medicine. He was Pathologist and Director of Laboratories at Touro Infirmary; Pathologist, New Orleans Hospital and Dispensary for Women and Children; and Consulting Pathologist to the U. S. Marine Hospital. He was a member and past president of the Orleans

Parish Medical Society; a member of the American Society of Clinical Pathologists; the American Medical Association; member of the Board of Directors of the American Society for the Control of Cancer; Chairman, Cancer Committee, Louisiana State Medical Society; and a Fellow of the American College of Physicians since 1927.

Personally, Dr. Lanford was a most delightful individual, who will be greatly missed by his many personal friends as well as by many professional admirers.

JOSEPH E. KNIGHTON, M.D., F.A.C.P.,
Governor for Louisiana

DR. CHARLES BENJAMIN WRIGHT

Charles Benjamin Wright, F.A.C.P., was born in Kemptiville, Ontario, Can., November 3, 1876 and died in Minneapolis, Minn., of myocarditis and emphysema on May 31, 1940. He moved to Grand Forks, N. D. with his parents and graduated from the University of North Dakota in 1898. He graduated from the Johns Hopkins University School of Medicine in 1902, following which he was House Officer of the Johns Hopkins University Hospital. After graduate study abroad in Vienna, Berlin and Rome in 1913 and 1914 he was appointed Associate Professor of Medicine at the University of Minnesota Medical School, a position which he held from 1920 to 1935. Dr. Wright had been Professor of Clinical Medicine at the University of Minnesota Medical School since 1935.

He was a member and past president of the Hennepin County Medical Society, member and past president of the Minnesota State Medical Association, member of the Minnesota Pathologic Society, Minnesota Academy of Medicine, Central Society for Clinical Research, Trudeau Society, Minnesota Society of Internal Medicine and a Fellow of the American College of Physicians since 1934. At the time of his death he was chairman of the Executive Committee of the Board of Trustees of the American Medical Association. Dr. Wright was the author of several articles dealing with rectal bleeding, histamine, undulant fever and microcytic anemia.

He was a prominent member of the University of North Dakota football team prior to his graduation and maintained his interest in athletics throughout his life, following with enthusiasm the progress of the University of Minnesota football team, and gaining reputation as a good bowler. Dr. Wright was friendly and loyal to those whom he respected and liked, and demonstrated his friendship at the cost of much time and energy to him. Because of his wide experience in administrative matters, his friends looked to him for advice and counsel in the organization of staffs and in the solution of problems connected with medical societies and hospitals. He was frank in his opinions, but when he disagreed with his associates, he disagreed tactfully with full consideration of the views of those who thought differ-

ently. He was fond of teaching and much interested in the younger members of the medical profession. Dr. Wright was indeed an excellent physician, a fine administrator, an important teacher and a valuable friend.

EDGAR VAN NUYS ALLEN, M.D., F.A.C.P.,
Governor for Minnesota

DR. JOSEPH CONDIT

Dr. Joseph D. Condit, F.A.C.P., aged 63 years, died at his home in Pasadena on July 5, 1940, following a long illness.

Dr. Condit was educated at Wabash College and was later honored by a Master's degree. He received his medical education at the College of Physicians and Surgeons of Columbia University, where he was graduated in 1901. He began practice in California in 1904 in Pasadena, where he has resided ever since. He was a member of many professional organizations, among which were the Los Angeles County, California State, and American Medical Associations and the American Heart Association. He had been a Fellow of the American College of Physicians since 1920. He was a diplomate of the American Board of Internal Medicine. He was a member of the attending staff of St. Luke's Hospital, and the Medical and Consulting staff of the Huntington Memorial Hospital, and formerly a member of its Board of Directors. During the World War Dr. Condit served as a major in the Medical Corps as regimental surgeon to the 79th Field Artillery. He was later made a Lieutenant-Colonel in the Reserve Corps. He was a member of the Pasadena University Club, and formerly a member of the Valley Hunt Club. Before his illness he enjoyed the activities of a number of social and civic organizations.

Dr. Condit in his long residence in Pasadena had grown up with the city, and was widely and well known by a host of friends who, with his family, feel the great loss they have sustained.

EGERTON L. CRISPIN, M.D., F.A.C.P.,
Regent.